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## REITER'S DISEASE

A STUDY OF 344 CASES  
OBSERVED IN FINLAND

*ILMARI PARONEN*

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FROM THE 56th WAR HOSPITAL AND THE KIVELÄ HOSPITAL, HELSINKI  
DIRECTOR PROFESSOR PAULI SOISALO, M. D.

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# REITER'S DISEASE

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BY

ILMARI PARONEN

HELSINKI 1948

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## PREFACE

Interest was stimulated in this work by a case of Reiter's disease observed by me at a field hospital on the Karelian Isthmus in Autumn 1943. The war gave me excellent opportunities of collecting material, but studying it thoroughly and from different aspects was, of course, more difficult than in normal circumstances. During the course of the investigation foreign literature — particularly English and American — was almost unobtainable. — The historical part of the work may seem too long to the reader, but as a uniform and comprehensive conception of the disease is difficult to obtain from previous studies of the subject, this length seems justified.

It is a great pleasure to thank my former chief and teacher, Professor P. Soisalo, M.D., Director of the Medical Department of the Kivelä Hospital, Helsinki. He helped me by arranging for the collection of the material and personally supervised my work in all its stages, giving me invaluable advice.

My sincere thanks are also due to my former chief and teacher, Professor Östen Holsti, M.D., Head of Medical Clinic III of the University of Helsinki, who has followed the progress of my work with unfailing interest and made valuable suggestions.

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I remember with gratitude all those colleagues, nurses, "Lottas", and others who have in many ways helped me in my work; among them particularly O. Helve, M.D., and A. Korhonen, M.D., Uni-

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Finally I wish to thank Miss Aino Wuolle, Mag. Phil., for translating the work into English.

Helsinki, September, 1947

Ilmari Paronen

## CONTENTS

	Page
DEFINITION AND NOMENCLATURE .....	7
HISTORICAL SURVEY .....	9
OBJECT OF THE INVESTIGATION; THE PROBLEM .....	37
MATERIAL AND METHODS .....	39
THE CLINICAL PICTURE OF REITER'S DISEASE .....	42
THE THREE CARDINAL SYMPTOMS .....	42
ARTICULAR INVOLVEMENT .....	44
MUSCLE AND TENDON INVOLVEMENT .....	50
OCULAR INVOLVEMENT .....	51
UROGENITAL INVOLVEMENT .....	53
PLEURISY .....	62
CARDITIS .....	63
OTHER LESIONS .....	66
FEVER .....	68
SEDIMENTATION RATE .....	71
OTHER BLOOD STUDIES .....	73
BLOOD PICTURE .....	73
DURATION OF REITER'S DISEASE .....	75
RECURRENCES .....	78
CONCURRENT DISEASES .....	79
DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS .....	82
PROGNOSIS .....	84
TREATMENT .....	85

	Page
ÆTIOLOGY AND PATHOGENESIS .....	88
AGE AND SEX .....	88
HISTORY .....	88
CONCURRENT DISEASES .....	90
DYSENTERY AND REITER'S DISEASE .....	90
SERO-BACTERIOLOGICAL STUDIES OF THE ÆTIOLOGY ..	95
DISCUSSION ON THE ÆTIOLOGY AND PATHOGENESIS ....	103
SUMMARY .....	106
REFERENCES .....	109

## DEFINITION AND NOMENCLATURE

Reiter's disease may be defined as a syndrome of unknown ætiology characterized by three essential symptoms, arthritis, conjunctivitis and urethritis. The syndrome is in most cases, but by no means always, post-dysenteric. The three cardinal symptoms — not always all present — form the framework of the syndrome which can be accompanied by other symptoms from almost any system.

Many names have been used for this disease; the most important are: *Rheumatismus intestinalis cum ulcere* (Cælius Aurelianus), *Arthritis* or *Polyarthritis dysenterica* (Huetle 1869, Korczynski 1874, Schittenhelm and Schlecht 1918, Manson-Bahr 1920, Kielland 1939, etc.), *Arthritis* or *Polyarthritis enterica* (Schittenhelm and Schlecht 1918, Tiemann 1932, etc.), *Ruhr-rheumatismus* (Dorendorf 1917, Walther 1940 c, etc.), *Ruhr-rheumatoid* (Schemensky 1918, Kempf 1944, etc.), *Arthritis* or *Polyarthritis urethritica* (Moltke 1936, Clemmesen and Kalbak 1938), *Syndrome conjunctivo-urétro-synovial* (Fiessinger and Leroy 1916), *Reiter's disease* (Musger 1934, Beck 1937, Hollander et al. 1945, Bergmark 1946, Feiring 1946, Löfgren 1946, Reimann 1946, Twiss and Douglas 1946, Vallee 1946, etc.), and *Spirochætosis arthritica* (Reiter 1916, 1917, 1921 and 1941, Frühwald 1927).

The names here enumerated are not particularly well-chosen as none of them expresses the essential in the disease, and each of them refers only to one or another of its features. The lack of a suitable name is mainly due to the fact that our knowledge of this syndrome is still in many respects limited.

In the present work the names Reiter's disease or syndrome and dysenteric arthritis are used, chiefly because they seem to be those most frequently employed. The former is to be considered rather inappropriate, as Reiter cannot be regarded as the first or even an important observer of the disease. However, this name is most widely used — in America exclusively — and so seems justified because it facilitates understanding of the concepts. Nor is the name dysenteric arthritis very well-chosen either, although, in a way, it describes the nature of the disease and its relation to dysentery. Thus it seems best to leave the name undecided until our knowledge of the ætiology and pathogenesis of the disease is wider.

## HISTORICAL SURVEY

According to Manson-Bahr (1943), articular complications following dysentery were known even to Cælius Aurelianus who lived at the beginning of the fifth century. Huette (1869) states that arthritides after dysentery had already been described by Zimmermann (1765), Lepecq de la Clôture (1765 and 1767), Stoll (1776 and 1777), and Thomas (1835). Cases of post-dysenteric joint disease were published before Reiter's time also by Gauster (1869), Korczynski (1874), Quinquand (1874), Rapmund (1874), and Remlinger (1898, 1901). As regards the other symptoms of the syndrome Stoll (1776—1777) reported dysuria in combination with arthritis and Remlinger (1901) observed acute nephritis in one of his cases besides arthritis. Kräuter (1871) described cases in which polyarthritis as well as conjunctivitis were noted after dysentery, and in Markwald's (1904) case all three symptoms, conjunctivitis, urethritis, and gonitis, appeared. Singer (1915), in addition to his cases of "dysenteric rheumatoid", reported cases of myalgia, neuralgia, conjunctivitis, and urethritis. Post-dysenteric syndromes were described in the same year as Reiter's (1916) case by Cahn, Dorendorf and Kollé, Fiessinger and Leroy, Rist, Crouzon, and Rose. In 1916 Walsch reported two cases without previous dysentery. One of these had urethritis, prostatitis and polyarthritis, the second urethritis and conjunctivitis. In the recent literature the writer has found over 80 reports dealing with Reiter's syndrome. The most extensive of them are Dorendorf's (1917) report of 59 cases. Schittenhelm and

Schlecht's (1918) of 140 cases, Walther's (1940 c) of 188 cases, Cimbal's (1942) of 114 cases, and Hollander's (1946) of 53.

Reiter's disease seems to have occurred in some measure in all European countries, also in the north, Denmark, Sweden, Norway, and in Finland where Thesleff (1937) has published one case. It has also been noted in India, Africa and America.

Not nearly all the published cases have been post-dysenteric. Perhaps just for this reason several investigators have avoided the adjectives *enterica* and *dysenterica* in naming the disease and published their cases as *Morbus* or *Syndroma Reiter*.

The frequency of the syndrome during epidemics of dysentery seems to vary greatly. The lowest and highest incidence figures given are 0.27 and 10 per cent (Dorendorf and Kolle 1916, Schlierbach 1941, Manson-Bahr 1943, etc.). It has also been noted that in one and the same locality the disease has appeared during one epidemic, but not during another, later one (Huette 1869, Manson-Bahr 1943). Further, observations have been made as to the nature of the dysentery later complicated by Reiter's syndrome. According to Dorendorf (1917), the dysentery in itself is then mild, whereas Walther (1941) considers that very mild and very severe cases do not lead to this complication. In Schittenhelm and Schlecht's (1918) series the dysentery and the subsequent polyarthritides were both severe in 20 per cent of the cases, in 32 per cent a mild dysentery was followed by a severe polyarthritides, and in 48 per cent both were mild. In addition there were 34 cases unaccompanied by any noteworthy enteritic symptoms, but as they were concurrent with the other cases, the cause was assumed to be the same. Attempts have also been made to discover what kind of dysentery causes Reiter's disease. In summarizing it may be stated that Reiter's syndrome seems to occur in toxic and non-toxic forms of bacillary dysentery, as it has been observed in Shiga-Kruse's dysentery (Markwald 1904, Cahn 1916, Sick 1918, Schittenhelm and Schlecht 1918, Manson-Bahr 1920 and 1943, Steenis 1931, Walther 1940 a and 1941, Krieger 1940, Cimbal 1942, Beiglböck 1943), in Flexner's dysentery (Kittsteiner 1915, Cahn 1916, Sick 1918, Worms, Lesbre and Sourdille 1927, Walther 1940 a and 1941, Kruspe 1941, Cimbal 1942, Beiglböck

1943, Kokko 1945), and in E-dysentery (Walther 1940 a and 1941). Arthritis complicating amœbic dysentery has also been described (Moorhead 1916, Manson-Bahr 1920).

Some authors consider that Reiter's disease does not occur in women, but only in young adult males (Löfgren 1938 and 1946, Arén and Lindgren 1945, Storm-Mathisen 1945, Twiss and Douglas 1946, Vallee 1946). However, Huette (1869), Gauster (1869), and Rapmund (1874) have noted forms with joint symptoms also in women, while Kräuter (1871) has observed in women the syndrome — conjunctivitis and arthritis — and Schittenhelm (1920) once — arthritis and vaginitis. Lever and Crawford (1944) and Young and McEwen (1947) have also each reported one female case; of Zewi's (1947) ten cases six were female and one a boy of 4.

As regards the order in which the essential symptoms appear it has been observed that any of these — arthritis, conjunctivitis or urethritis alone or in any combination — may initiate the disease. According to the literature, however, the triad does not evolve in nearly all cases, but the disease may also occur with two or even one essential symptom. Yet both ocular and urethral lesions seem to occur relatively seldom alone or together as the only sign of the syndrome. On the contrary, joint lesions appear in several series in the majority of cases as the only symptom, at times even in all cases. The diagnosis has then been based on the fact that the joint disease had appeared following a dysentery, or, if not, cases of dysentery and Reiter's triad had occurred in the environment.

## ARTHRITIS

In the clinical picture of Reiter's disease articular affections seem to predominate and are extremely seldom absent. They generally appear after the symptoms of dysentery have subsided, more rarely while they are still present (Huette 1869, Gauster 1869, Kräuter 1871, Quinquand 1874, Schittenhelm and Schlecht 1918, Ganténberg 1939). According to Walther (1940 a and 1941), the joint symptoms may occasionally be observed even during the period of incubation and appear one to

two days before the enteritic symptoms or simultaneously with them. He uses the name "Frühhreumatismus" with reference to these cases as distinct from "Spätrheumatismus" with a later onset. However, the interval between the dysentery and Reiter's disease may even be some months. In one case reported by Zewi (1947) it was two months and Kräuter (1871) observed post-dysenteric arthritic symptoms four months after the disappearance of bloody diarrhoea. In this case, however, the dysentery had been followed by chronic colitis and it is thus possible that the dysentery was of unusually long duration.

According to Dorendorf (1917) and Schittenhelm and Schlecht (1918), the great majority of the cases began within two to four weeks from the onset of dysentery.

In the great majority of cases the arthritis seems to be poly-articular in character. Thus Schittenhelm and Schlecht's series consists of 124 poly- and 12 monarthritides. The different joints become involved at the same time or successively. The joint feels tender on movement and there is spontaneous pain particularly at night. Later, articular swelling and effusion appear and occasionally the affected joint also becomes hot (Gauster 1869, Schittenhelm and Schlecht 1918, Balban 1934, Hollander *et al.* 1945, Jackson 1946, Wrigley 1946, *etc.*) and red (Gauster 1869, Schittenhelm and Schlecht 1918, Balban 1934, Hollander *et al.* 1945, Feiring 1946, Jackson 1946, Twiss and Douglas 1946, Vallee 1946, *etc.*). The severity of the effusion seems to vary considerably from case to case and also in the different joints of the same patient. Thus the joints may sometimes be only very slightly swollen, while sometimes — for instance when the knee joint is involved — unbearable pain may be caused by the excessive formation of synovial fluid in the joint cavity (Schittenhelm and Schlecht 1918, Beiglböck 1943, *etc.*). Occasionally the clinical picture may resemble that of gonorrhoeal arthritis (Huette 1869, Brugsch 1930, Hollander *et al.* 1945) or of gout (Schittenhelm and Schlecht 1918).

The clinical manifestations described by Dorendorf (1917) differ from the above in that he reports no redness of the affected joints.

According to the literature, there has been a form of the disease in which no evident or recognizable changes in the joints were observed and articular pain was the only symptom (Schittenhelm and Schlecht 1918, *etc.*). Remlinger (1898) distinguishes two main types of articular involvement: the polyarticular type with migratory pain and the hydrarthrodial type, resistant to all therapy. He states that the two forms may appear concurrently in the same patient. Walther (1940 c) similarly divides these articular affections into two groups, "Arthralgia" and "Gelenkrheuma". His series of Reiter's disease includes 64 of the former and 46 of the latter.

Articular suppuration has not occurred, according to the literature. Although Huette (1869) states that earlier researchers have commented on such cases, these suppurating joints can hardly be associated with Reiter's disease and are probably due to secondary infection arising in consequence of aspiration or some other factor, *e.g.* a concurrent suppurative process (Cf. p. 80).

According to Remlinger (1898), Schittenhelm and Schlecht (1918), Stühmer (1921), *etc.*, the synovial exudate is yellowish, viscous, only slightly turbid, and fibrinous; it has an albumen content of 1.3—4 per cent (Esbach), contains more fibrin the older it is, and the inflammatory cells are chiefly polymorphonuclears. Vallee (1946), on the other hand, states that the number of lymphocytes practically equals that of the polymorphonuclear cells. Beiglböck (1943) reports that in his series the aspirated fluid contained from 1,000 to 5,000 leucocytes per cu. mm. and Hollander *et al.* (1945) obtained 9,000 to 14,000 leucocytes per cu. mm.; of them 65—70 per cent were neutrophils.

Writers agree in all essentials regarding the frequency of involvement of the different joints. It is thus evident that in the great majority of cases the joints of the lower extremities are more commonly affected than those of the upper, and the large joints much more often than the small joints (Dorendorf 1917, Stettner 1917, Schittenhelm and Schlecht 1918, Cimbal 1942, Beiglböck 1943, Hollander *et al.* 1945). This is illustrated in the table below showing the distribution of joint involvement in Schittenhelm and Schlecht's 136 cases:

Joints involved	No. of cases	Joints involved	No. of cases
Knee .....	137	Spine .....	7
Ankle .....	107	Sternoclavicular .....	6
Wrist .....	41	Sacrum .....	6
Shoulder .....	33	Temporomandibular .....	5
Elbow .....	23	Metacarpal .....	4
Toe .....	23	Metatarsal .....	4
Finger .....	22	Art. acromioclavicularis .....	2
Hip .....	20	Larynx .....	1

According to Huette (1869) and Dorendorf (1917), the articulations of the right side seem to be affected somewhat more often than those on the left. Dorendorf further reports his observation that the weight-bearing joints are more likely to be involved than those subject to less strain. Yet his series seems to be too small to warrant such a conclusion.

Some investigators hold that the course of the arthritis resembles the migratory type of polyarthritis seen in rheumatic fever (Kräuter 1871, Korczynski 1874, Feiring 1946, Vallee 1946, Pinck 1947). Most observers consider, however, that there is no migration of symptoms from one joint to another.

The duration of arthritis seems to vary considerably from case to case, according to the literature. Thus, in some patients, the joint lesions may disappear within a few days, yet in the majority they last for weeks or months (Huette 1869, Gauster 1869, Stühmer 1921, Twiss and Douglas 1946, *etc.*). In the series of Hollander *et al.* (1945) the duration varied from three to eight months, but in some cases there were symptoms even after eight months. Schittenhelm and Schlecht (1918) state that arthritic symptoms have been observed in a few extremely rare cases for as much as two years. Dorendorf (1917) watched the course of the disease in 12 patients from the onset to the disappearance of symptoms and found that it lasted from 35 days to 12 months, in one case more than one year.

The literature seems to contain comparatively few statements as to the recurrence of arthritis. This may be due to the fact that most investigators have dealt with soldiers on active duty and the patients were mostly transferred during the course of

treatment from hospitals in the theatre of operation to the home area. Consequently, in the vast majority of the cases it has not been possible to follow the course of the disease to the end, and there are no data regarding possible recurrences. According to Quinquand (1874), dysenteric arthritis leaves no predisposition to recurrence; some recent observers, however, have reported recurrence of the joint complications (Cf. p. 32).

Involvements of the bursae, tendons, tendon sheaths and synovial membranes are closely related to the articular symptoms. They may be concurrent with the joint disease or appear independently, the joints remaining unaffected (Dorendorf and Kolle 1916, Dorendorf 1917, Stettner 1917, Schittenhelm and Schlecht 1918, Sick 1918, Stühmer 1921, Paetzel 1928, Raschewskaja 1935, Gantenberg 1939, Walther 1941, Kempf 1944, etc.). Schittenhelm and Schlecht's (1918) series contained six cases of tendovaginitis and four of periostitis. On X-ray examination Hollander *et al.* (1945) noted periosteal proliferation in three cases, but radiographs taken later showed that it had disappeared in two of them.

Muscular pain seems also to occur in connection with Reiter's disease (Gauster 1869, Cahn 1916, Rose 1916). This so-called "Muskelrheuma" appeared in 116 of Walther's (1940 c) 188 cases. Schemensky (1918) has noted a persistent "muscular rheumatism" in 2 per cent of his cases during convalescence from dysentery, and Kokko (1945), in his series from Finland, muscular pain in 52 per cent at the acute stage of dysentery. The latter high percentage may, however, include cases in which the pain may be attributed to the same causes as in acute fever in general.

Röntgen studies of the affected joints have shown osteoporosis and slight signs of bone destruction, occasionally also periosteal proliferation (Frühwald 1927, Paetzel 1928, Salvesen 1937, Hollander *et al.* 1945, Feiring 1946, Sjöberg 1946, Twiss and Douglas 1946, Vallee 1946, Pinck 1947). These changes did not appear until two months after the onset (Hollander *et al.* 1945, Twiss and Douglas 1946) and were most pronounced in the small joints where also ankylosis was noted (Paetzel 1928, Twiss and Douglas 1946).

## OCULAR LESIONS

According to reports in the literature, eye affections are generally concomitant with the arthritis (Kräuter 1871, Dorendorf and Kolle 1916, Schittenhelm and Schlecht 1918, Manson-Bahr 1920, Walther 1940 c, etc.), but sometimes the former are accompanied by lesions of the urinary tract only (Waelsch 1916, Dorendorf 1917, Stühmer 1921, and Beiglböck 1943), or appear quite alone (Dorendorf 1917, Manson-Bahr 1920, Kokko 1945). Ocular affections may also initiate the disease and the arthritis appear later (Dorendorf 1917, Stettner 1917, Schittenhelm 1920, and Beiglböck 1943). Variable figures of incidence have been reported for the eye affections. Of 610 patients with dysentery recorded by Steenis (1931) twelve developed eye symptoms, of Holler's (1941) 1,620 patients 21, and of Kokko's (1945) 555 patients 111. About one-half of Kokko's patients showed inflammatory changes in the *conjunctiva sclerae*. Two of his patients had a concomitant arthritis and urethritis and several showed the triad — eye pains (or mild conjunctivitis), joint pain, and "burning" on urination. More often still two symptoms appeared together, the most common combination being eyes and joints; that of eyes and urethra was much less frequent, and that of urethra and joints was observed only in a few cases. Dorendorf (1917) reports that conjunctivitis unaccompanied by arthritic or urethritic symptoms occurred as a complication of dysentery in 3 per cent of his cases. He gives the incidence of conjunctivitis in Reiter's disease as 25.5 per cent, whereas 29 per cent is quoted by Schittenhelm (1920), 68 per cent by Gounelle *et al.* (1941), 82 per cent by Cimbal (1942), and 4.5 per cent by Walther (1941).

Conjunctivitis, either bilateral or unilateral, seems to be the most common ocular manifestation. In bilateral cases it may start in both eyes simultaneously or first in one and later in the other eye. The degree of severity varies greatly, from quite mild injection of the conjunctivæ to an intense purulent conjunctivitis which latter may be attended by marked chemosis, œdema of the lids, and a tendency of the lids to stick (Kräuter 1871, Dorendorf 1917, Schittenhelm and Schlecht 1918, Sommer

1918, Stühmer 1921, Walther 1940 c and 1941, Kokko 1945, etc.). Besides a redness of the conjunctiva, episcleral hyperæmia has often been noted; to this has been attributed the deep purple colour characteristic of the conjunctivitis seen in Reiter's disease.

Cases of iritis, keratitis, corneal ulceration, and irido-cyclitis have also been described (Reiter 1916, Dorendorf 1917, Stettner 1917, Schittenhelm and Schlecht 1918, Sick 1918, Manson-Bahr 1920, Stühmer 1921, Worms *et al.* 1927, Brugsch 1931, Cimbal 1942, Haarr 1945, Hollander *et al.* 1945, Tengroth 1945, Bergmark 1946, Feiring 1946, Jackson 1946, Vallee 1946, Wrigley 1946, Zewi 1947). Optic neuritis was noted in two cases by Zewi (1947); in one there was also a conjunctivitis and in the other a kerato-iritis.

On microscopical examination the ocular exudate was found to contain a large number of leucocytes and few epithelial cells, the results of the bacteriological examination being either negative or showing only a few cocci (Schittenhelm and Schlecht 1918, Sommer 1918, Stühmer 1921, Kruspe 1941, Feiring 1946, Twiss and Douglas 1946, etc.).

There are only a few statements in the literature regarding the duration of the eye affections, e.g. that the conjunctivitis generally lasts for a few days or weeks, rarely longer (Stettner 1917, Schittenhelm and Schlecht 1918, Sommer 1918, Hollander *et al.* 1945, Jackson 1946, Twiss and Douglas 1946). One and a half to four months has been mentioned as the duration of iritis and keratitis (Stühmer 1921, Zewi 1947). Recurrences of the eye affections have also been reported (Kräuter 1871, Stettner 1917, Stühmer 1921, Cimbal 1942), even years after complete recovery (Vallee 1946, Twiss and Douglas 1946).

## UROGENITAL INVOLVEMENT

According to most observers, diseases of the urinary system occupy the third place in the symptom triad. Urethritis is considered the commonest and occurs in Schittenhelms and Schlecht's (1918) series in 6 per cent, in Gounelle's *et al.* (1941) in 47 per cent, and in Cimbal's (1942) in 63 per cent

of the cases. According to Walther (1940 c), cases of urethritis (9 per cent) are more frequent than conjunctivitis (3.4 per cent). Kokko's (1945) series from Finland included only three cases of purulent urethritis, whereas 90 patients had "pain on micturition" and one half of them had also noticed that, although the output of urine was as usual, voiding was more difficult and the urinary stream poorer. As stated earlier (p. 15), Kokko's series consisted of cases observed during the acute stage of dysentery, and, consequently, they cannot all be considered Reiter's disease. Urethritis may occur as the initial symptom of the syndrome (Dorendorf 1917, Stettner 1917, Schittenhelm 1920, Beiglböck 1943, Hollander *et al.* 1945, Twiss and Douglas 1946, Vallee 1946, *etc.*), and it has been observed also as the only symptom (Dorendorf 1917, Arén and Lindgren 1945).

The urethral discharge seems to be less profuse than in acute gonorrhœa and it is in most cases observed only on pressure of the penis. It is reported to vary from sero-purulent to thick purulent and it may also contain blood. The urethral meatus is often described as swollen and red and its mucous membrane as slightly pouting (Singer 1915, Reiter 1916, Stettner 1917, Schittenhelm and Schlecht 1918, Sommer 1918, Stühmer 1921, Frühwald 1928, Balban 1934, Clemmesen and Kalbak 1938, Gounelle *et al.* 1941, Hollander *et al.* 1945, Jackson 1946, Twiss and Douglas 1946, Vallee, *etc.*). Microscopical examination has shown a large number of leucocytes but few epithelial cells. Bacteriological findings have been negative or only non-pathogenic organisms have been found (Singer 1915, Sommer 1918, Stühmer 1921, Frühwald 1928, Clemmesen and Kalbak 1938, Hollander *et al.* 1945, Feiring 1946, Twiss and Douglas 1946, Vallee 1946, *etc.*).

Affections of the bladder have also occurred (Cahn 1916, Sick 1918, Hoff 1940, Cimbal 1942) and the series of some investigators have included even cases of cystitis of which a considerable part have been hæmorrhagic (Reiter 1916, Dorendorf 1917, Sommer 1918, Stühmer 1921, Holler 1941, Bauer and Engleman 1942, Beiglböck 1943, Colby 1944, Arén and Lindgren 1945, Haarr 1945, Miller and McIntyre 1945, Twiss and Douglas 1946, Pinck 1947). Bergmark (1946) has described two cases of cystitis more

closely, one of the patients having had a gonococcal urethritis about one month previously; recovery had been complete, however. In these cases hæmaturia, especially a terminal hæmaturia, was noted and in one of them also coagula. Cystoscopy revealed that the capacity of the bladders was 50 to 75 c.c., the mucous membrane was highly œdematous, bullous in places, partly covered by "fibrin", and bled easily.

As to renal disease Remlinger (1901) has noted acute nephritis once in connection with dysenteric arthritis and Schittenhelm and Schlecht (1918) similarly once. Remlinger's case was studied also patho-anatomically and the changes observable in acute glomerulo-nephritis were found. The nature of the disease in the latter case was not studied in detail. The authors only state that, besides a marked hæmaturia, albumin was found in the urine, and in the urinary sediment there were large numbers of white and red blood cells, a few granular casts and epithelial cells. In addition to pyelonephritis and cystitis, Colby (1944), in one case, diagnosed hydronephrosis and in another "renal dilatation" and hæmaturia. Slight albuminuria and pyuria were present also in one of Twiss and Douglas's (1946) cases, in Feiring's (1946) both cases, and in two of Zewi's (1947) cases. In the instance reported by Wrigley (1946) there was slight albuminuria but nothing pathological in the sediment. Otto (1940) and Hoff (1940) state that they have noted renal colic in a total of three cases.

Prostatitis has been recorded a few times in connection with Reiter's syndrome (Waelsch 1916, Wiedmann 1934, Clemmesen and Kalbak 1938, Bauer and Engleman 1942, Haarr 1945, Hollander et al. 1945, Miller and McIntyre 1945, Vallee 1946, Pinck 1947), and prostatic abscesses a few times (Colby 1944, Arén and Lindgren 1945). Tiemann (1932) describes a case of orchitis and Sick (1918) one of epididymitis. Ten out of Kokko's (1945) 555 patients with dysentery complained of testicular pain which was extremely persistent in some cases.

The presence of urethral strictures observed by Twiss and Douglas (1946), in one of their patients should be mentioned. This is attributed to a first attack of the disease two years pre-

viously. The urethritis involved also the prostate and the bladder, whereas the upper urinary tract was normal on intravenous urography.

According to most observers, the affections of the urinary system last for a few days or weeks, but may occasionally persist as long as four months (Stettner 1917, Stühmer 1921, Bergmark 1946, Sjöberg 1946, Twiss and Douglas 1946, etc.), and recurrence has been observed even several years after complete recovery (Stühmer 1921, Hollander *et al.* 1945, Twiss and Douglas 1946, Vallee 1946, etc.).

### LESIONS OF THE NERVOUS SYSTEM

In connection with this syndrome symptoms have been observed also in the central and peripheral nervous system, and the commonest of these seems to be neuritis (Cahn 1916, Schittenhelm and Schlecht 1918, Steenis 1931, Holler 1941). In Walther's (1941) series neuritis occurred as a post-dysenteric complication in 0.7 per cent of the cases. Wilke (1943) observed polyneuritis both concomitant with the other symptoms of Reiter's disease and alone. The polyneuritis was usually localized in the nerves of the proximal muscles comprising the shoulders, the pelvic region and also the abdominal muscles (*e.g.* the *m. deltoideus*, *serratus*, *supra-* and *infraspinatus*, *ileopsoas*, *quadriceps*, *glutæus*). In severe cases of polyneuritis Wilke observed that the distal nerves of the extremities were also occasionally affected and then there were, besides muscular paralysis, disturbances of sensibility characteristic of the distal type of neuritis; in the proximal type sensory disturbances could be entirely lacking at first. Wilke (1943) further noted changes in the cerebrospinal fluid in severe cases; the albumin content was higher than normal but the number of cells was normal or only slightly increased. Zewi (1947) noted two cases of optic neuritis. — Neuralgias have also been described (Singer 1915, Rose 1916, Walther 1941, etc.). The most frequent localizations reported are the *trigeminus*, *occipitalis*, *frontalis*, *supraorbitalis*, *intercostalis*, *ulnaris*, *radialis*, *medianus*, *ischiadicus*, *saphenus*, and *tibialis*.

## CARDIAC INVOLVEMENT

There is some disagreement as regards the occurrence of cardiac complications. Some observers state that heart complications are absent in Reiter's disease (Quinquand 1874, Raschewskaja 1935, Hoff 1940, Zewi 1946), while others hold the opinion that endocarditis and valvular disease do not occur, but myocarditis does (Dorendorf and Kolle 1916, Schemensky 1918, Steenis 1931, Otto 1940, Holler 1941). A few investigators have also reported cases of endocarditis. Thus Stettner (1917) comments on lesions of the endo- and myocardium. According to Rose (1916), Castin and Fradet have published a case of mitral disease complicating dysenteric arthritis and Trousseau a case of endo-pericarditis. Beiglböck (1943) reports a case of mild mitral endocarditis, and Bergmark (1946), in one instance, considers the diagnosis of endocarditis established. Gauster (1869) noted a left-sided exudative pleurisy once and, as an additional finding, exudative pericarditis as complications of post-dysenteric arthritis. A systematic electrocardiographic study of patients with dysenteric arthritis has not been made. However, a number of electrocardiographic tracings have been obtained by a few investigators; some of them noticed no abnormalities (Salvesen 1937, Kielland 1939, Walther 1940 b, Miller and McIntyre 1945, Twiss and Douglas 1946), while others observed changes which indicate myocardial damage (Beiglböck 1943, Bergmark 1946). In Vallee's (1946) case electrocardiographic changes appeared during the treatment: the P-R interval was prolonged to 0.26 second and there was at the same time a slight rise of the S-T segment in leads 2 and 3. In Feiring's (1946) two cases the P-R interval varied from 0.18 to 0.24 second in several tracings recorded during the treatment.

It should be added that Dorendorf and Kolle (1916) called attention to the occurrence of bradycardia and Schittenhelm and Schlecht (1918), Schemensky (1918), Hoff (1942), and Manson-Bahr (1943) to that of tachycardia in this disease. Schemensky (1918) attributes the tachycardia to slight toxic injury to the heart muscle or to nervous disorder. Walther (1940 b) states, on

the other hand, that tachycardia occurs as a late symptom in about 1 per cent of patients with dysentery. The tachycardia, which generally starts during convalescence on the 16th to 25th day after the onset of the disease, he considers a sign of an allergic phenomenon in the organism.

### RESPIRATORY SYSTEM

Among diseases of the respiratory tract complicating Reiter's syndrome, cases of dry and exudative pleurisy have been described (Gauster 1869, Schittenhelm and Schlecht 1918, Sick 1918, Holler 1941, Cimbal 1942); the pleurisy has usually been mild (Schittenhelm and Schlecht 1918). In Gauster's (1869) case referred to earlier (p. 21) there was, in addition to a left-sided pleurisy, also an exudative pericarditis, but other instances suggestive of a possible polyserositis have not come to the author's attention. Further, some cases of bronchitis have been reported (Cahn 1916, Schittenhelm and Schlecht 1918). In Walther's (1940 c) series bronchitis occurred in 13.8 per cent of the cases. Schittenhelm and Schlecht (1918) reported some instances of epistaxis concurrent with the other symptoms and in the series of Gounelle *et al.* (1941) these amounted to 32 per cent. Gounelle ascribes the epistaxis to prolongation of the coagulation time. Cases of rhinitis and pharyngitis have also been noted (Feiring 1946, Vallee 1946).

### DIGESTIVE SYSTEM

As stated already, diarrhoea is present in the great majority of cases. It cannot, however, be regarded as a symptom of Reiter's disease but should rather be looked upon as an antecedent disease mainly on the following grounds: (1) it occurs almost without exception before the onset of the cardinal symptoms of the syndrome, antedating them usually by some weeks, at times even months; (2) The diarrhoea in these cases has not differed in any way from the epidemic diarrhoea occurring on each occasion in the same locality. — Apart from this diarrhoea involvement of the digestive system seems to be extremely rare. Thus

only twice has a palpable spleen been reported (Reiter 1916, Schittenhelm and Schlecht 1918) and twice a spleen enlarged to percussion (Balban 1934, Pfleger 1937). At times jaundice has been observed together with dysenteric arthritis, but as its nature and course have not differed from ordinary catarrhal jaundice, it has evidently been only a coincidental disease (Schittenhelm and Schlecht 1918, Tiemann 1932, Hoff 1940).

### OTHER LESIONS

Involvement of glands other than the sex glands already mentioned has been reported a few times. Thus Sick (1918), Manson-Bahr (1920 and 1943), Otto (1940), Hoff (1940), and Holler (1941) have noted parotitis, Sick (1918) and Kokko (1945) inflammation of the submandibular gland, Sick (1918) two cases of inflammation of the lacrimal gland and two of the mammary gland. In Reiter's disease the lymph nodes have also frequently been involved, enlargement of the axillary and inguinal nodes being observed (Moltke 1936, Usseglio and Zancan 1940), Bauer and Engleman (1942). Twiss and Douglas (1946) and Feiring (1946) have both published a case in which the cervical, axillary, epitrochlear, and inguinal nodes were enlarged. Microscopical section showed a non-specific type of hyperplasia of the inguinal lymph node (Twiss and Douglas 1946).

Besides redness of the urethral meatus other cutaneous changes have also been observed on the penis. Cases of balanitis have been described occasionally (Sick 1918, Clemmesen and Kalbak 1938, Cimbal 1942, Beiglböck 1943, Hollander *et al.* 1945, Wrigley 1946, *etc.*). Furthermore, typical eczema has been noted on the glans and the prepuce (Postma 1937, Beck 1937, Kuske 1939, Kruspe 1941, Hoff 1942, Hollander *et al.* 1945, Sargent 1945, Feiring 1946, Jackson 1946, Twiss and Douglas 1946, Vallee 1946). These lesions may appear as small, sharply margined erythematous spots covered with a brown crust (Kruspe 1941, Vallee 1946, Feiring 1946, *etc.*) or as small yellowish vesicles or superficial ulcerations occasionally with a narrow light-coloured

edge; the lesions may also be coalescent (Beck 1937, Twiss and Douglas 1946, *etc.*). Lesions of a similar kind may, according to Twiss and Douglas (1946), appear also in the conjunctivæ, the cornea, hard palate, pharynx, scrotum, and palms of the hands. Of other skin lesions may be mentioned hyperkeratotic eruptions on the extremities and the trunk (Rost 1911, Wiedmann 1934, Kuske 1939, Kruspe 1941, Hollander *et al.* 1945, Storm-Mathisen 1945, Feiring 1946, Jackson 1946, Twiss and Douglas 1946, Pinck 1947). Kuske (1939) states that these lesions are erythematous and papular at first, but later pustular efflorescences surrounded by a narrow inflammatory margin develop. Finally crusts arise which are hyperkeratotic in appearance and the eruption most closely resembles *rupia*. Histologic examination revealed parakeratotic hyperkeratoses, serofibrinous exudate, and large numbers of small pus cells. On the soles the lesion seems to appear as small pustules with hyperkeratosis of the overlying skin (Twiss and Douglas 1946), and the finger nails may be raised by hyperkeratotic collections. Changes in the nails appear at the same time. They become long, thickened and brittle, and the nail fold grows markedly (Rost 1911, Twiss and Douglas 1946). Urticaria has also been observed in dysenteric arthritis (Walther 1941, Holler 1941); erythema exsudativum multiforme (Cahn 1916, Rose 1916), and hæmorrhagic eruptions (Gaussel 1936, Cahn 1916, Schittenhelm and Schlecht 1918) are rare occurrences. In the mouth cavity lesions have appeared (*stomatitis aphthosa* and *ulcerosa*, glossitis) either associated with skin lesions or without them (Cahn 1916, Rose 1916, Schittenhelm and Schlecht 1918, Hoff 1940, Feiring 1946, Twiss and Douglas 1946). Local œdema has been described (Schemensky 1918, Sick 1918, Hoff 1940), and Holler (1941) considers it Quincke's œdema. A few cases of otitis externa have also been reported in connection with Reiter's disease (Steenis 1931, Wrigley 1946).

It is difficult to say whether all the skin lesions here enumerated can be ascribed to Reiter's disease, or whether they are concurrent lesions due to other causes. At any rate it should be borne in mind that there may be considerable difficulty in differentia-

ting Reiter's disease from *keratosis blennorrhagica* and from the so-called Stevens-Johnson syndrome.

## FEVER

The fever in Reiter's disease seems to be subject to great variation. Thus there has been high fever in some cases, while in others only a slight rise of temperature has been observed and even afebrile cases have been reported (Huette 1869, Quinquand 1874, Kräuter 1871, Dorendorf and Kolle 1916, Dorendorf 1917, Schittenhelm and Schlecht 1918, Hoff 1940, etc.). The maximum axillary temperature most often reported is  $39.5-40^{\circ}\text{C}$ . (Schemensky 1918, Stühmer 1921). According to Rose (1916), the maximum axillary temperature varied from  $37$  to  $37.4^{\circ}\text{C}$ . in subacute polyarthritis in which the only symptom was articular pain, from  $37.8$  to  $38.2^{\circ}\text{C}$ . in acute monoarthritis, and from  $37$  to  $39$  and  $39.5^{\circ}\text{C}$ . in acute polyarthritis. In cases of "muscular rheumatic disease" Schemensky (1918) observed a rise of temperature to  $37.5^{\circ}\text{C}$ . in only one, the temperature being normal in the others. — As regards the nature of the fever it is reported that the remissions are generally great in the types with high fever, the temperature being in the morning  $37^{\circ}\text{C}$ . and in the evening  $39-40^{\circ}\text{C}$ ., and the duration of the fever may vary from a few days to five months (Gauster 1869, Rose 1916, Reiter 1916, Stettner 1917, Sommer 1918, Stühmer 1921, Hollander *et al.* 1945, Jackson 1946, Twiss and Douglas 1946, etc.).

Opinions differ on the occurrence of sweating. Kräuter (1871), Balban (1934), and Cimbal (1942) report that in connection with the joint disease the patients experience severe sweating especially at night, but in Rapmund's (1874) series this was completely absent. Several others have observed that there is often no sweating or it is mild in degree (Dorendorf 1917, Schittenhelm and Schlecht 1918, Schittenhelm 1920), or occurs only at an early stage of the disease and often intermittently (Quinquand 1874). No definite mention of chills has been found. However, one of Gauster's (1869) cases started suddenly with chills; in the series of Hollander *et al.* (1945) no chills appeared.

## BLOOD STUDIES

According to the literature, the sedimentation rate is generally increased and varies from 14 to 140 mm. in one hour by the Westergren method (Raschewskaja 1935, Moltke 1936, Postma 1937, Clemmesen and Kalbak 1938, Kielland 1939, Cimbali 1942, Stoia 1943, Beiglböck 1943, Miller and McIntyre 1945, Storm-Mathisen 1945, Bergmark 1946, Feiring 1946, Zewi 1947). Hollander *et al.* (1945) observed that an increased sedimentation rate generally became normal in about three months. In one of the cases reported by Twiss and Douglas (1946) the sedimentation rate remained normal in spite of ocular and urethral symptoms; during the period when articular symptoms were present the rate was increased.

Systematic studies of the blood picture seem to be fairly infrequent. On the basis of the few reports it appears that, in general, the red cell count has been normal (Moltke 1936, Clemmesen and Kalbak 1938, Beiglböck 1943, Miller and McIntyre 1945, Feiring 1946, Jackson 1946, Vallee 1946, Wrigley 1946). However, Twiss and Douglas (1946) have noted secondary anaemia in two cases and Storm-Mathisen (1945) in one. The white cell count has generally shown leucocytosis, but in some cases it has been normal. The number of leucocytes has varied from 4,800 to 21,000 per cu. mm. (Schittenhelm and Schlecht 1918, Stühmer 1921, Moltke 1936, Salvesen 1937, Postma 1937, Kielland 1939, Beiglböck 1943, Hollander *et al.* 1945, Miller and McIntyre 1945, Bergmark 1946, Feiring 1946, Jackson 1946, Twiss and Douglas 1946, Vallee 1946, Wrigley 1946, *etc.*). The differential count remained within normal limits except for an occasional eosinophilia or "shift to the left". Thus Moltke (1936) has once noted an eosinophilia of 6 per cent, Beiglböck similarly of 6 per cent, while in Twiss and Douglas's (1946) cases eosinophils varied from 2 to 28 per cent, the total number of leucocytes ranging from 9,700 to 19,300. The degree of the "shift to the left" has been slight, the values for the juvenile neutrophils varying from 2 to 3 per cent (Beiglböck 1943) and those for rod

in 37, in 3 of whom there had been no diarrhoea. Positive agglutination tests for dysentery have been obtained also from the synovial exudate (Worms *et al.* 1927, Gounelle *et al.* 1941) in titres from 1:100 to 1:400 (Worms *et al.* 1927). In a few cases serum agglutination tests for typhoid, paratyphoid, and *B. abortus* were made, but agglutination could not be demonstrated (Kristjansen 1930, Kielland 1939, Miller and McIntyre 1945, Feiring 1946, Twiss and Douglas 1946, Vallee 1946, *etc.*). In one instance Kruspe (1941) observed that the serum agglutinated *B. abortus* in titres of 1:400.

### PATHO-ANATOMICAL CHANGES

Postmortem examination has been performed, according to the literature, in three cases. Remlinger (1901) noted in his two cases that the process in the knee joint was limited to the synovial membrane, although the disease had lasted for months. The synovium was thickened and its surface slightly opaque, the other soft parts and bone surfaces were of ordinary appearance. In one of these cases in which there had been an associated acute nephritis, each kidney weighed 350 grammes. The capsule was easily detached, the underlying surface appeared pale, greyish. The cortex was thickened. The medullary substance was dark red and its colour was clearly distinguishable from that of the cortex. Microscopical examination showed marked glomerulitis and focal hæmorrhages in the cortex as well as in the medullary substance. Fatty degeneration was observed in the cells of the tubulus contortus. Wepler (1942) has post mortem examined one case in which intestinal hæmorrhage was the cause of death. The hæmorrhage was due to the rupture of a submucosal blood vessel in the stomach; the cause of the rupture was not definitely revealed by microscopical study. The cartilages of the knee joint appeared normal and the articular cavity contained greenish yellow fluid. Microscopical examination revealed an œdematous synovium and disappearance of the superficial synovial cells. Lymphocytic infiltrates were present in the joint capsule and the periarticular tissue. The greater part of the cells

of the synovial exudate were polymorphonuclears. Nothing pathological was observed in the cartilage and the bone. In Wepler's opinion the process is non-specific and distinct from infectious and rheumatoid arthritis.

Bauer and Engleman (1942) performed an arthrotomy of the knee joint and observed formation of villi in the suprapatellar bursa. In a biopsy of the articular synovium the intima was found to be composed of several layers of cells and its lymphocytes and plasma cells were moderately increased, even the leucocytes to some extent. There were no corpuscular findings and no exudate. Throughout the subintimal layers there was also a mild, diffuse inflammatory cell infiltration. A marked hyperæmia was present in the synovium. Hollander and his co-workers (1945) also carried out an arthrotomy of the knee joint on a patient whose disease had lasted for eight months; the findings were as follows: Synovium greatly thickened, congested, and purple in colour. Lying on its surface were several small, circumscribed areas of white fibrinous-like material. The cartilages appeared normal. Microscopical examination showed intense inflammatory reaction limited to the superficial synovial layers. The synovium had large club-like projections which contained numerous dilated capillaries. Each projection was distended by a heavy lymphocytic infiltrate mixed with a few plasma cells and neutrophils. No exudate was observed. The intima was approximately six to ten layers deep. Only a few perivascular focal collections of lymphocytes and plasma cells were found. There were no new capillaries and the intense hyperæmia seemed to consist in dilatation of pre-existing capillaries. In the biopsy of an enlarged inguinal lymph node Twiss and Douglas (1946) found a moderate plasma cell infiltration and Storm-Mathisen (1945) chronic lymphadenitis.

## TREATMENT

In the treatment of dysenteric arthritis the same principles have generally been followed as in the treatment of rheumatic fever. It has been noted, however, that salicylates and pyramidon

have little or no effect (Schittenhelm and Schlecht 1918, Schemensky 1918, Frühwald 1927, Kruspe 1941, Beiglböck 1943, *etc.*). Neosalvarsan, collargol, arthigon, and milk injections have also been used (Sommer 1918, Schittenhelm and Schlecht 1918, Stühmer 1921, Frühwald 1927, Stoia 1943), all with negative result. Only Beiglböck (1943) observed in ten cases treated with arthigon that a shifting of the pain to other joints stopped at least after the third injection, the pain subsided, the exudate diminished, and the conjunctivitis disappeared rapidly but the urethritis more slowly. In his opinion the rise of temperature seemed to be the essential feature of arthigon therapy; if there was no rise, the treatment seemed to be of no avail. Yet even in such cases a fever induced by pyriferin seemed to influence the course of the disease favourably. Rose (1916) reports that he has obtained very good results with anti-dysenteric serum and Schemensky (1918) states that serum treatment has given relief of pain and improved the mobility of the joints, although they did not seem to be less swollen, as in Rose's cases. Beiglböck (1943) and Stoia (1943), on the other hand, have obtained no positive results even with large doses of anti-dysenteric serum. Klemperer and Strisower (1920) report similar findings when using "Kruse's vaccine". Stoia (1943) states that he has obtained good results with injections of the patient's own blood treated with short waves, and with solganal. Sulphonamides (Beiglböck 1943, Hollander *et al.* 1945, Miller and McIntyre 1945, Twiss and Douglas 1946, Bergmark 1946, *etc.*) and penicillin (Hollander *et al.* 1945, Miller and McIntyre 1945, Bergmark 1946, Twiss and Douglas 1946, Feiring 1946, *etc.*) have hitherto proved of no effect in the treatment of Reiter's syndrome.

## DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

In Reiter's disease the diagnosis has not generally been considered difficult, as it is readily distinguished from other joint diseases by the associated symptoms. As already stated (p. 24), there may occasionally be considerable difficulties in differentiating the condition from *keratosis blennorrhagica* and the

Stevens-Johnson syndrome. This is chiefly due to the circumstance that, most recently, cases of Reiter's disease have been observed with skin lesions similar to those seen in *keratosis blennorrhagica* (Lever and Crawford 1944, Hollander *et al.* 1945, Twiss and Douglas 1946, Feiring 1946, Jackson 1946) and that, on the other hand, cases of the latter disease have occurred in which urethritis, arthritis and dermatitis have been accompanied by inflammation of the eyes (Lojander 1928, Chambers and Koetter 1933, Combes *et al.* 1940). Although a careful history-taking and the gono-reaction may often decide the diagnosis, it seems that the exact correlation of the two diseases is not yet clear. Freireich, Schwartz and Steinbrocker (1947) consider that they might be variants of the same disease and that gonorrhœal infection in *keratosis blennorrhagica* might be "a predisposing agent in the causative process actually producing pictures of both diseases and their variants". Stevens-Johnson's or Behcet's syndrome, on the other hand, comprises an aphthous or ulcerating stomatitis, ulcerations in the genitalia or around the anus, at times also urethritis, eye lesions, such as conjunctivitis, iritis, retinitis, and even hypopyonuveitis. In most cases there are also skin lesions, generally of the type *erythema exsudativum multiforme*. In many instances recurrences are noted. As some of these symptoms may be lacking and, on the other hand, also inflammatory joint disease may occur (Halonen and Klemola 1947), it is possible that a clinical picture resembling Reiter's syndrome may develop in certain cases.

### PROGNOSIS

The prognosis *quo ad vitam* is good in Reiter's disease; up to the present it has not as such led to death in a single case. According to Huette (1869), earlier observers have reported cases which ended fatally, but the uncertainty of the diagnosis and of the causal connections make it improbable that these data can be seriously considered. In general the disease does not cause permanent or disabling changes in the affected organs. Yet there have been a few cases of permanent damage to the eye (Vallee

1946) and of ankylosis of the joints (Paetzel 1928, Raschewskaja 1935, Lever and Crawford 1944, Twiss and Douglas 1946, Vallee 1946), and one case of urethral strictures has been reported (Twiss and Douglas 1946).

### DURATION AND RECURRENCE

Recovery is usually spontaneous. The duration varies in the reports of different observers, being generally, however, two to five months. Recurrences (Cf. p. 14) are seldom reported in the literature apparently because conditions have made sufficiently long observation of the cases impossible (most of the reported cases occurred in soldiers during World Wars I and II). Recurrence was noted in Freund's (1928) case ten years, in Storm-Mathisen's (1945) case seven and twelve years, and in one of Twiss and Douglas's (1946) cases two years after the initial illness. In Kardung's (1941) case there were several recurrences over a period of 15 years, in Sjöberg's (1946) case over a period of 5 years, and in Vallee's (1946) case of 16 years. Hollander (1946) states that recurrences appeared in 15 per cent of his cases.

### ÆTIOLOGY AND PATHOGENESIS

Although a great number of studies have been published the ætiology and pathogenesis of Reiter's disease are still largely obscure. On the other hand, many positive observations have also been made on which future studies may be based.

The majority of researchers have held the opinion that Reiter's syndrome is causally closely related to dysentery (Huette 1869, Korczynski 1874, Dorendorf 1917, Schittenhelm and Schlecht 1918, Kruspe 1941, Walther 1940 c) or to other enteritic infections (Singer 1925, Tiemann 1932, Musger 1934, Pflieger 1937) which in most instances precede the essential symptoms of the syndrome. Yet — especially judging from German and American reports — it is evident that in some of the cases there has never been a dysentery or enteritis; therefore it has also been assumed that dysentery is not the sole, although perhaps the most usual cause of Reiter's syndrome. In the cases without diarrhœa it has

been supposed that the infection may enter by way of the genitalia (Waelsch 1916, Michael 1917, Paetzel 1928, Kristjansen 1930, Beck 1937, Thesleff 1937, Kuske 1939, Kardung 1941, Haarr 1945). Other portals of entry, for instance dental foci (Stoia 1943), furuncles (Junghanns 1918) *etc.*, have been more rarely suggested.

In the cases without diarrhoea the disease has been assumed to spread for instance through sexual connection (Waelsch 1916, Kristjansen 1930, Beck 1937, Löfgren 1943). In this respect Kristjansen's case is of particular interest. The patient developed a non-specific urethritis and arthritis one month after intercourse with a girl who was known to suffer from vaginal discharge, which had repeatedly proved negative for gonococci. The girl also had a relationship with another man who also acquired a non-specific urethritis, though without arthritis.

Reiter's finding of a spirochæte seems to have aroused particular interest and caused special investigations with a view to revealing the ætiology of the syndrome. Reiter (1916) made blood cultures from his patient in blood ascites broth and found in a two-day-old culture an organism which he believed to be a spirochæte; its movement was characterized by "a boring rotation and no flexion". For this reason Reiter called it *Spirochæte forans*. Mice inoculated with this culture died suddenly on the 8th to 10th day. On guinea pigs the culture had no effect and neither in these nor in mice was this spirochæte subsequently demonstrated. Reiter, however, believed that he had found the causative agent and therefore proposed *Spirochætosis arthritica* as the name of the syndrome. Later it was suggested that the so-called spirochæte of Reiter may not have been the causative organism but an incidental cultural finding (Sick 1918, Stühmer 1921, *etc.*). Besides Reiter, Macfie (1917) has only once found spirochætes in the urethral pus.

There have been other noteworthy bacterial findings. Worms *et al.* (1927) report that in stained specimens of aspirated synovial fluid in four severe cases they found a great number of polynuclear cells and clumps of "gram-negative cocci", but cultures yielded no growth. The aspirated fluid agglutinated dysentery bacilli in titres of 1:100—1:400. Musger (1934) obtained a non-

sexual and sexless, and they change their form. In one form they are filterable, like viruses, in another they may exactly resemble bacteria, also as regards conditions of growth.

It is naturally too early to draw far-reaching conclusions from the studies of Dienes, yet the value of Reiter's and Macfie's observations of spirochaetes will be quite different if Dienes's findings are confirmed. In any case the work of Dienes requires serious consideration in all future studies of Reiter's syndrome.

It may be added that the consistently negative results obtained in numerous bacteriological tests have given rise to the hypothesis of virus causation (Beck 1937, Löfgren 1938, 1943 and 1946, Arén and Lindgren 1945).

Some investigators have assumed that the syndrome is caused by metastases (Vossius 1904, Dorendorf 1917, Brugsch 1931, *etc.*) or by toxins produced by the dysentery bacillus (Remlinger 1898, Dorendorf 1917, Steenis 1931, *etc.*). The observation, rare as it is, of *B. dysenteriae* also in the patient's blood in dysentery would seem to suggest the former possibility. Thus Posselt (1928) found in the literature a total of 140 cases in which blood cultures yielded *B. dysenteriae*. However, these organisms were in most cases found only at the onset of dysentery or during the period of incubation. In the cases described above (p. 34) *B. dysenteriae* was obtained from the synovial fluid; this seems to support the theory of a metastatic origin. Schittenhelm and Schlecht (1918) consider that the disease cannot be ascribed to dysenteric toxins, as it appears at a time when the bowel wall ought already to be healed and consequently there should be no more toxin in the body, and as it also occurs in cases in which enteritic symptoms are entirely lacking. In their opinion there would still remain the possibility of an enteric infection caused by other kinds of spores whose toxins might play a part in the causation.

Attempts have been made to explain the pathogenesis of Reiter's disease on the basis of the theory of allergy, analogously with that of rheumatoid arthritis (Löfgren 1938, Walther 1940 a, b, c, 1941, *etc.*). Schittenhelm and Schlecht (1918) are opposed to this opinion, as they observed no allergic reaction when dysentery patients were injected with dysenteric vaccine or toxin.

Walther (1940 a, b, c, 1941) considers it likely that dysenteric arthritis is an allergic disease but does not regard it simply as a complication of dysentery, as it often appears already in the first week of disease, even one to two days before the enteritic symptoms, at a time when the causative agent of dysentery cannot yet have sensitized the organism; he supposes that some other antecedent disease — a previous dysentery, rheumatic fever, scarlet fever, gonorrhœa, sinusitis, angina, *etc.* or a focal infection, might have sensitized the organism beforehand and that the dysentery, encountering this already "charged" system, would — in a way — make the disease "burst out". "*Frühhreumatismus*", accordingly, would be a parallergic reaction appearing chiefly as arthralgias and myalgias, whereas "*Spätrheumatismus*", commencing in the third to fourth week of disease and often as a severe polyarthritis, would probably be accounted for by a specific allergic reaction.

Finally there are the skin reaction tests carried out by Storm-Mathisen (1945) with synovial exudate and lymph node emulsion obtained from a patient with Reiter's disease. Within forty-eight hours there was a reddish infiltrate in the area of injection in the patient himself and in four others with the same disease. In the control cases the result was negative. On account of the small number of cases and in the absence of required additional studies it seems that no conclusions can be drawn as to the specificity of the reaction.

## OBJECT OF THE INVESTIGATION; THE PROBLEM

The review of the literature given in the previous chapter will have shown that the disease known as dysenteric arthritis or Reiter's syndrome has attracted the interest of investigators for several decades and that numerous studies have been published dealing from different aspects with the clinical picture, ætiology, pathogenesis, prognosis, and treatment of this disease. Agreement has already been reached on many questions concerned with this syndrome, but — on the other hand — many others of essential importance still remain obscure. A study of the disease has evidently been rendered more difficult by its comparatively rare occurrence and the fact that most cases have appeared in war time, when conditions have been particularly favourable for the spread of dysentery but the opportunities for scientific study also more limited than in times of peace.

Although observers agree in all essentials as to the clinical picture of Reiter's disease, it is notable that opinions vary regarding questions so important as cardiac and pleural involvement and the tendency of the disease to recur. Different data have also been published on questions of less importance, for instance the migration and external manifestations of the arthritis, the occurrence of skin lesions, sweats etc. It is also noteworthy that, up to the present time, there have been no systematic studies of the *blood picture, electrocardiogram etc.* in this disease. — Most of the disagreements and deficiencies here mentioned seem to be due to the small number of cases generally dealt with in the publica-

tions, a series often comprising only from one to ten cases; thus the observer may have had a too limited view.

However, the greatest disagreement seems to prevail on the ætiology and pathogenesis. While some consider that dysentery is the basic disease and can be so even in cases without dysentery, others hold that Reiter's syndrome is no disease *sui generis*, but a syndrome caused by different infectious diseases and infections. It has also been ascribed to Reiter's spirochæte, virus infection, and most recently, to pleuropneumonia-like organisms. As regards the pathogenesis Reiter's syndrome has been ascribed to bacteria, bacterial metastases or toxins, invasion being by way of the intestines, the urethra or some other point, but it has also been regarded as an allergic disease.

Thus our knowledge of Reiter's disease is still defective in many respects and further study of the subject seems necessary and desirable. As there were a great number of cases — almost an epidemic — in Finland in 1943 and especially during the widespread dysentery of 1944, a closer study and the publication of the material (344 cases) thus obtained has seemed advisable, the more so as no more extensive series than this has hitherto been published.

On the basis of what has been stated in the review of the literature the writer has here chiefly sought an answer to the following questions:

1. *What is the clinical picture and prognosis of Reiter's disease?*
2. *Does the material available throw additional light on its ætiology and pathogenesis?*

## MATERIAL AND METHODS

The present series comprises a total of 344 cases (see Table 1). Of these the hospital reports of 10 have been lost, so that the actual material consists of 334 cases. The great majority (322 cases) are from the Defence Forces and were observed in 1943 and 1944. There are also 22 civilian cases from 1945 and 1946, of whom 13 were treated at Medical Clinic II of the University of Helsinki, one at the Children's Clinic, one at the Out-Patient Department for Internal Diseases, and two cases at the Medical Department of the Kivelä Hospital; five cases are from the writer's private practice.

In the autumn of 1943 a Corporal was admitted to the 31st Field Hospital with a severe, sterile conjunctivitis and urethritis, and indefinite pain in the knees. The case aroused surprise, until — after the knee joints had swollen — Reiter's syndrome was diagnosed. Similar cases appeared later in other places and the patients were collected, at the end of 1943, at Medical Clinic II of the University of Helsinki which had been converted into a War Hospital. During 1944 such cases were collected at the 56th War Hospital at Nokia; Medical Clinic II had been evacuated to this place in February 1944. On the Karelian Isthmus, where most of the cases occurred, the patients were first collected chiefly at Field Hospital 31 where some mild cases were treated and then returned fit for duty to their units. Those requiring prolonged treatment were evacuated to War Hospital 56, and at the end of 1944 those still in need of treatment were transferred to the 10th Hospital for Disabled Servicemen at Tampere. Some of these patients were later admitted to Medical Clinic II in Helsinki and a few to the Hospitals for Disabled Servicemen in their communal areas.

During all this time Prof. P. Soisalo was the Head of Medical Clinic II and War Hospital 56 and he personally investigated the cases and supervised the examinations and therapeutical measures. The writer too had the opportunity of examining and personally treating the greater number of the patients during the entire course of their illness, and each patient at least at some stage, while working at Field Hospital 31, War Hospital 56, the 10th Hospital for Disabled Servicemen, and Medical Clinic II. The methods of study and observation have thus been most uniform. A great advantage was the well-equipped laboratory of the hospital, although war-time conditions caused certain difficulties and prevented the use of some planned methods of investigation. All the patients were subjected to the closest possible clinical examination and the course of the disease was followed from day to day. The methods used will be described when discussing the results.

Table 1 shows the year the illness started and the age and sex distribution of the patients.

TABLE 1	
YEAR OF ONSET WITH AGE AND SEX OF PATIENTS	
In 1943 .....	11 cases
„ 1944 .....	311 „
„ 1945 .....	21 „
„ 1946 .....	1 „
Total .....	344 cases

Age, Years	Men	Women	Total
2 .....	1	—	1
12—15 .....	3	—	3
16—20 .....	29	5	34
21—30 .....	166	12	178
31—40 .....	102	8	110
41—50 .....	9	8	17
55 .....	—	1	1
Total .....	310	34	344

The material is in some measure one-sided in that it comprises for the most part previously healthy 18 to 40 year old men fit

for duty and women of about the same age and physical condition who served in the forces, but only few civilians. The figure in the preceding table, consequently, do not give an all-over picture of the question concerned.

The sero-bacteriological studies were carried out partly in the Department of Serology and Bacteriology in the University of Helsinki, partly in the Bacteriological Laboratories of the Defence Forces, and, in addition, a considerable part of the bacteriological tests and cultures were made in the laboratories of each hospital. Studies of vitamins were carried out in the Department of Medical Chemistry of the University of Helsinki.

## THE CLINICAL PICTURE OF REITER'S DISEASE

### THE THREE CARDINAL SYMPTOMS

The incidence of the three cardinal symptoms of Reiter's disease, i.e. of articular, ocular, and urogenital affections, is shown in Table 2 where + denotes that the organ is affected, and — that it is unaffected.

TABLE 2  
OCCURRENCE OF THE THREE CARDINAL SYMPTOMS OF THE SYNDROME

Joints	Eyes	Urogenital system	Total No. of cases	%
+	+	+	233	69.8
+	+	—	56	16.8
+	—	+	24	7.2
—	+	+	4	1.2
+	—	—	12	3.5
—	+	—	5	1.5
—	—	+	0	0
Total 325	298	265	334	100
% 97.3	89.2	79.3		

As seen from Table 2, the complete triad — affections of joints, eyes, and urethra — is the most common type in the author's series which in this respect corresponds to several earlier publications. On the other hand, this series differs from some reports published earlier in that the incidence of ocular and urogenital involvements is high (*Cf.* pp. 16 and 17). Cases with only urethral lesions are entirely lacking in this material which, however, may

depend also on the fact that such cases were not sent to the hospitals mentioned above but treated elsewhere.

In the great majority of the cases (69.1 per cent) the onset was monosymptomatic; the initial symptom was urethritis in 23.9, arthritis in 23.3, and conjunctivitis in 21.9 per cent of the cases. In less than 1/4 of the cases the onset was bisymptomatic, the two initial symptoms appearing during the same day. Involvement of eyes and urinary system was the most common combination, the next in order lesions of eyes and joints, while the urinary tract and the joints were seldom simultaneously involved. Less than 8 per cent of the cases showed the entire triad at the onset; all the three cardinal symptoms appearing on the first day of the disease. Each of the three cardinal symptoms occurred on the first day of the disease, alone or in any combination; eye involvements in 48.6 per cent, urethritis in 47.3 per cent, and arthritis in 42.8 per cent.

The present material corresponds to those reported by Doren-dorf (1917), Schittenhelm (1920), Beiglböck (1943) etc. in that the disease may begin with any of the three essential symptoms; it is not, however, possible to compare numerical data because they are lacking in earlier investigations.

In the cases with only one or two initial symptoms some new essential symptom could appear as late as more than a hundred days after the onset. Thus a case appearing mono- or bisymptomatic at first could later become bi- or trisymptomatic. In the great majority of cases (71.4 per cent), however, all the cardinal symptoms appeared during the first ten days after the onset of the syndrome. This is seen from Table 3 which shows the time — in ten-day periods — during which the complete triad or two symptoms of it developed.

*In the writer's series of Reiter's disease all three cardinal symptoms were thus present in 69.8 per cent of the cases, 25.2 per cent showed two symptoms, and 5.0 per cent only one symptom. Cases with only urethral lesions were not observed. Any of the three cardinal symptoms, or any combination of the three, were present at the onset. More than 2/3 of the cases had only one initial symptom, less than 1/4 had two initial symptoms, and*

less than 8 per cent showed the complete triad at the onset. In about 71 per cent of the cases a clinical picture with three or two symptoms developed during the first ten days of the disease, in the others later, even as late as one hundred days after the onset.

TABLE 3  
PERIOD DURING WHICH THE COMPLETE TRIAD OR TWO SYMPTOMS  
OF THE SYNDROME EVOLVED

Days	No. of cases	%
1—10 .....	224	71.4
11—20 .....	43	13.7
21—30 .....	20	6.4
31—40 .....	12	3.8
41—50 .....	7	2.3
51—60 .....	2	0.6
61—70 .....	2	0.6
71—80 .....	1	0.3
81—90 .....	2	0.6
101—110 .....	1	0.3
Total .....	314 <sup>1)</sup>	100

<sup>1)</sup> Three cases are omitted because the clinical report did not reveal the length of this period.

### ARTICULAR INVOLVEMENT

In addition to the usual methods of examination, a new one has been used to discover the presence of fluid in the knee joint. This method, of which the author has found no description in the literature, seems to be suitable in cases in which the amount of fluid is so small that ballottement of the patella is difficult to notice. The method is as follows: The patient lies on his back relaxed, the knee joint extended and its front and inner aspect well illuminated. By moving the patella the examiner makes sure that the patient does not strain the femoral muscles, and then presses the medial excavation of the knee until any fluid which has collected there is pressed out. Immediately after that the area between the lateral excavation and the upper recess is pressed; all the fluid in the joint now flows back to the medial side and this is recognized by a distinct swelling of the medial excavation, a visible reflux of fluid. The simplest way of carrying out the test is as follows; the examiner grasps the knee of the patient from the proximal side so that the patella remains between the thumb and the forefinger. The medial excavation is pressed with the thumb and all four fingers, the area of the lateral excavation and the upper recess with

the palm. If the exudate is old it may move so sluggishly to and fro that alternate pressure on the medial and lateral excavation may be required several times until there is a reflux of fluid. This phenomenon is probably caused by the greater viscosity of old exudate or by adhesions that may have developed in the joint cavity and which at the beginning of the test may prevent the moving of the fluid.

Joint manifestations were present in 325 cases (97.3 per cent). Of these 316 (97.2 per cent) were polyarthritic and only 9 cases (2.8 per cent) monarthritic. The arthritis generally began in one or several joints with tenderness upon movement or touch. Some patients felt only stiffness on moving the joint. Spontaneous pain, too, appeared in most cases after a day or two. In some patients (17.5 per cent) the joint affection was of arthralgic type during the whole disease, but in the majority (82.5 per cent) it was associated with articular swelling; all the affected joints or only some of them became swollen while the others remained of arthralgic type. Table 4 shows the distribution of the material into three such groups as well as the relation between poly- and monarthrititis.

TABLE 4

## ARTICULAR INVOLVEMENT

	Arthritis	Arthralgia	Arthritis and arthralgia combined	Total
Polyarthritic .....	44	55	217	316 = 97.2 %
Monarthritic .....	7	2	—	9 = 2.8 %
Total .....	51	57	217	325
	15.7 %	17.5 %	66.8 %	

In Table 5 is seen the frequency of involvement of different joints, the incidence of swelling and arthralgia, and the changes in skin colour observed in the swollen areas. The frequency of joint involvement corresponded largely to data in earlier reports (Cf. p. 13), but in the present series there was no noticeable difference between the joint manifestations of the right and left side, as pointed out by Huette (1869).

TABLE 5

FREQUENCY OF JOINT INVOLVEMENT, RELATION BETWEEN ARTHRITIS AND ARTHRALGIA, AND ALTERATIONS IN SKIN COLOUR IN 324 CASES

Joint	Total No. of affected joints	Arthritis	Arthralgia	Joints with changes in skin colour
Knee .....	448 = 25.4 %	315	133	—
Ankle .....	286 = 16.2 %	196	90	62
Toes <sup>1)</sup> .....	142 = 8.0 %	109	33	57
Shoulder .....	137 = 7.8 %	6	131	—
Wrist .....	114 = 6.5 %	61	53	6
Fingers <sup>1)</sup> .....	114 = 6.5 %	76	38	19
Metatarsal <sup>1)</sup> ....	109 = 6.2 %	83	26	34
Sacrum <sup>1)</sup> .....	106 = 6.0 %	—	106	—
Elbow .....	86 = 4.9 %	14	72	3
Hip .....	74 = 4.2 %	2	72	—
Vertebral, lumbar and thoracic <sup>1)</sup> .	50 = 2.8 %	—	50	—
Vertebral, cervical <sup>1)</sup> ....	27 = 1.5 %	—	27	—
Metacarpal <sup>1)</sup> ....	25 = 1.4 %	19	6	6
Sternoclavicular ..	15 = 0.8 %	11	4	—
Acromioclavicular	13 = 0.7 %	—	13	—
Temporo-mandibular ....	12 = 0.7 %	—	12	—
Sacroiliac .....	7 = 0.3 %	1	6	—
Tibiofibular .....	1 — (0.1 %)	1	—	—
Total No. of joints	1766 = 100 %	894	872	187

<sup>1)</sup> Considered as one joint although several joints were affected.

In about 60 per cent of the cases the different joints became involved within 20 days calculated from the day the first joint became affected to the day the last became involved. However, there were cases in which new joints became involved even several months after the onset of the first articular symptoms. This is illustrated in Table 6 showing the distribution of the cases according to ten-day periods.

TABLE 6

PERIOD DURING WHICH THE DIFFERENT JOINTS OF A PATIENT  
BECAME INVOLVED

Time in days	No. of cases
1—10 .....	112
11—20 .....	69
21—30 .....	37
31—40 .....	28
41—50 .....	14
51—60 .....	10
61—70 .....	7
71—80 .....	4
81—90 .....	3
91—100 .....	4
101—110 .....	—
111—120 .....	4
121—130 .....	2
131—140 .....	5
Ca. 7 months .....	2
„ 11 „ .....	1
Total .....	302

In the majority of cases the tenderness of the joints was relatively mild. The patient was able to move the swollen joints and to stand. There was generally only partial limitation of movement; in some cases the joints could even be freely moved and pain was felt only at the extreme range of motion. Active movements were always more painful than the passive. In a few patients the tenderness was so severe that the joints could be moved only very little, and the pain in the joints resembled greatly that seen in gonorrhœal arthritis. These cases also showed a great tendency to contractures and muscular atrophy. Spontaneous pain in the joints was often very marked at the onset and seemed to be due, in most cases, to distention of the bursæ or of the joint capsule by the heavy exudation. In some patients, on the other hand, the spontaneous pain was slight and was felt particularly at night. In the morning several patients complained of a stiffness of the joints which, however, decreased

considerably during the day, or even disappeared entirely. Swelling of the joints generally appeared during the first days of the disease simultaneously with the pain and tenderness, but in some cases there was pain and tenderness even several weeks before the joints became swollen. Swelling of the knee joint was invariably due to the presence of exudate in the joint cavity or the bursæ and not to periarticular œdema. In the elbow joint exudate was found in only three cases. In the other joints fluid was not noted on clinical examination, and the swelling then seemed to consist of a periarticular œdema which varied somewhat in severity and firmness according to the localization and the individual. Thus intense swelling often occurred on the ankle joint where the region of the medial or lateral malleolus might be swollen, the other side of the joint appearing normal. On the dorsum of the foot and the back of the hand the œdema was also intense and softer than elsewhere. In the finger and toe joints spindle-shaped swelling was observed. In the knee joint a large amount of exudate generally developed in the early stage of gonitis, causing intense and painful distention. The exudate was yellowish with a slight tinge of green, viscous, and usually somewhat turbid. Its specific gravity varied from 1.020 to 1.022 (six cases) and the range of the pH was from 7.5 to 10.0 (14 cases). In 2/3 of the examined patients (30 cases) the exudate contained between 4 and 5 per cent albumen, the minimum being 1 per cent and the maximum 12 per cent (Esbach). In the majority of the cases the cells of the exudate consisted chiefly of neutrophil granulocytes, their percentage amounting even to 90 per cent. In some instances, however, lymphocytes predominated, varying from 57 to 74 per cent. Monocytes represented 1 to 2 per cent. The amount of eosinophil cells ranged from 0 to 53 per cent (seven cases).

Further, it was observed that certain joints were swollen in none of the cases, some very seldom, others again comparatively often, and that the swelling in certain joints consisted of a periarticular œdema, while in others the presence of exudate seemed responsible for it. This variety seemed to depend mainly on anatomical construction of the joint and on the quantity and quality

of the surrounding tissues. In the knee joint, for instance, there are large bursæ which communicate with the joint cavity and are able to hold a large amount of exudate; the knee joint also contains places where the tissues surrounding the joint readily yield to pressure from the inside. An articular structure of this kind facilitates the formation of exudation, as is seen for instance in the fact that exudate develops more slowly if, after aspiration, a tight bandage is applied. On the other hand, in a joint surrounded by unyielding tissue like tendons and aponeuroses a recognizable exudate cannot develop, and the exudative process leads rather to a periarticular swelling. If the joint lies deep in the tissues and especially if covered with muscles — as for instance the joints of the vertebral column — even this œdema cannot be clinically recognized.

In 187 articulations (Table 5) changes occurred in the colour of the skin, but only in five cases (twice in the knee and three times in the ankle) was the skin definitely hot. The colour alterations occurred in the swollen areas where the skin appeared dirty grey, although a purple or reddish component was often observed at first. In addition to swelling and a purple colour, numerous petechiæ appeared in one case in the ankle area and on the dorsum of the foot, lasting for 17 days. — Unfortunately, no studies of the blood coagulation were carried out in this case.

X-ray examination of the different joints was made in 76 cases, altogether 156 times. The knee was examined 67 times, ankle and metatarsal joints 53, wrist and metacarpal region 11, elbow 6, fingers 6, shoulder 5, and toes 4 times, hip twice, heel and cervical vertebræ both once. In the great majority of cases (66 in number) the examination was carried out within one month after the particular joint had become involved; in only nine patients within two to four months, and in one case one year after the disease began. In none of the cases were the röntgenological findings abnormal. In this respect the present material differs from earlier reports (Cf. p. 15), but this is probably due to the fact that X-ray examination was carried out at a time when röntgenological changes were not yet present. Because of

a shortage of films it was unfortunately not possible to submit our patients to follow-up examinations.

The present series resembled those reported earlier in that the pain in the affected joints was persistent and did not move from joint to joint, as is characteristic of rheumatic fever (*Cf.* p. 14). The amount of exudate and the severity of the symptoms varied to some extent, but generally the disease remained localized to the joints once involved and disappeared only gradually. In some instances the pain and tenderness in a particular joint, or even several, lasted only for a few days, but the more intense symptoms with the associated swelling were generally localized to a single joint or a few joints and persisted for a long time. Several patients complained of increased pain and tenderness of the affected joints in cold and wet weather.

#### MUSCLE AND TENDON INVOLVEMENT

The articular symptoms were accompanied by tenderness and pain in the scapular region in 45 cases, in the side in 26, the muscles of the limbs in 26, the heel in 13 (once associated with swelling), the Achilles tendon in seven (five associated with swelling), the tuberosity of tibia in five, and the spina iliaca anter. superior in three cases. The series included no cases showing the single symptom of muscular pain. The pain in all the locations mentioned was usually mild and troubled the patients especially at night, thus disturbing their sleep. The tenderness felt by the patients in these areas caused more discomfort. It could prevent deep breathing, render walking difficult and so on. The roentgenological findings in these cases were negative, also in one case in which the insertion of the Achilles tendon had been swollen and tender for 4 ½ months. The symptoms described above usually lasted for a comparatively short period, a few days or weeks. An exception was the case in which the insertion of the Achilles tendon was affected; the region was definitely swollen and slightly tender on pressure even two years later.

## OCULAR INVOLVEMENT

The series of 334 patients included 298 cases (= 89.2 per cent) with eye symptoms. Table 7 shows the types of ocular involvement.

TABLE 7

### OCULAR INVOLVEMENT

Diagnosis	No. of cases	Remarks
Conjunctivitis acuta .....	239	11 unilateral cases
Keratoconjunctivitis .....	13	7       "       "
Iritis .....	11	7       "       "
Keratoiritis .....	10	7       "       "
Ulcus simplex corneæ .....	4	
Iridocyclitis .....	1	
Total .....	278	
Feeling speck in eye, epiphora and purulent discharge without noticeable redness .....	20	
Total No. of cases .....	298 = 89.2 %	

As seen from Table 7, the majority of the eye affections were diseases of the conjunctiva and obviously conjunctivitis had been present also in all others. In only two cases was irido-conjunctivitis the primary ocular diagnosis, and in one kerato-conjunctivitis. Even these were not noted until about five days after the onset of the eye symptoms. In all other cases involvement of the iris and the cornea was preceded by a conjunctivitis which had either become entirely asymptomatic or at least improved considerably in between. The asymptomatic interval varied from ten days to 17 months (*Cf.* p. 78). These cases are not included in the group of conjunctivitis in Table 7; they have been separated into a special group of iridic or corneal involvement. Examination of the eye grounds was carried out in very few cases of conjunctivitis but regularly when the iris and cornea were affected. The eye grounds were normal in all examined cases.

The conjunctivitis was bilateral in all except 11 cases. In most cases (4/5) the conjunctivitis began in both eyes at the same time. In about 1/5 of the cases the other eye became affected later, generally after one to two days, but occasionally

after more than two months. The first symptoms of conjunctivitis were a feeling of something in the eye, smarting, photophobia, and epiphora. This was soon attended by redness of the conjunctivæ and a mucopurulent discharge. The lids often stuck in the morning. Swelling of the lids appeared often but was generally slight; in few cases was intense swelling observed. The eyes of one patient were absolutely "walled up" owing to very intense swelling as far as the anterior part of the auricle, and swelling remained intense for five days. Both the *conjunctiva palpebræ* and *bulbi* were a deep cranberry red and had a velvety surface. The redness varied in degree, being rather slight in some cases but mostly intense and occasionally attended by a marked chemosis, which partially covered the cornea. In some instances the symptoms were milder in one eye than in the other during the whole course of the disease. This characteristic colour of the conjunctiva and its velvety surface were most marked at the onset of the conjunctivitis and were in the author's opinion sufficiently marked to be used as an aid to diagnosis. The muco-purulent discharge was generally thin, greyish, but there were also cases in which it was purulent, even very thick. On microscopical examination the conjunctival discharge showed leucocytes, and stained specimens were negative in all cases except one in which a few gram-negative cocci were discovered. Gonococcal cultures also yielded no growth. It is to be regretted that no differential leucocyte count was made. In only one case was an eosinophil count carried out: eosinophils amounted to 46 per cent, the other cells being chiefly neutrophils. The duration of the conjunctivitis varied from a few days to seven months. However, in most cases the conjunctivitis disappeared in one to four weeks (*Cf. p. 77*).

In the cases of *keratitis* there were both superficial and deep infiltrates, varying from round shapes, 1—2 mm. in diameter, to large pleomorphic figures. Besides such small infiltrates there appeared in one case a long and narrow bow-shaped ulcer in the cornea. The duration of *keratitis* varied from one to four months (*Cf. p. 77*).

The symptoms of *iritis* were conjunctival and pericorneal redness and discoloration of the iris. Slight precipitation was only

seldom noted in the anterior chamber, but there was a strong tendency to form posterior adhesions and therefore iris pigment was often found on the surface of the lens. Once there was blood in the anterior chamber. The duration of iritis varied from one to five months (Cf. p. 77).

## UROGENITAL INVOLVEMENT

In each case the urine was tested for sugar and albumin. The former test was always negative. In a total of nine cases albumin was found (Cf. p. 56, nephropathies). Besides these investigations the urine obtained with catheter was examined in 40 cases. In 305 cases the urethral meatus and the adjacent parts were carefully washed with water and soap and immediately after this the patient passed most of the urine from the bladder, the last part into a sterilized dish. These tests were carried out once or several times (maximum 5) at weekly intervals. All urine specimens were free from albumin and sugar; the reaction was generally acid, the  $pH$  being in about one-half of the cases 5.5, in one-fourth 5, in one-fifth 6, and in about one-tenth the range of the  $pH$  was from 6.5 to 7. In five cases an alkaline urine reaction (litmus) was occasionally obtained. The microscopical examination revealed nothing pathological in the sediment. Stained specimens of catheter urine were negative for bacteria. Cultures of the catheter urine specimens from 30 patients once or several times were negative in 29 cases and one yielded *S. paratyphi B.* (Cf. p. 98). The other urine specimens were also generally negative to the Gram stain. In only six cases were found the non-pathogenic bacteria which are usually present in the urethra (so-called epithelial bacteria). In 169 cases the urinary sediment was stained for tubercle bacilli with negative result.

Diseases of the urogenital system were noted in 265 cases which corresponds to 79.3 per cent of the whole series. Table 8 gives a detailed analysis of the number and nature of these diseases.

TABLE 8

## UROGENITAL INVOLVEMENT

Urethritis alone .....		103 cases
combined with:		
Macular eczema on the penis .....	63 cases	
"      "      and suppuration on the penis ..	6 "	
"      "      "      ulcerations "      "      "	5 "	
Ulcerations on the penis .....	3 "	
Margins of meatus and adjacent parts reddened	24 "	
Dysuria .....	12 "	
Hæmaturia .....	4 "	
Nephropathy .....	9 "	
Involvement of testes or epididymis .....	9 "	135 cases
	Total	238 cases
		(= 89.8 %)
No clinically recognizable urethritis; other symptoms as follows:		
Macular eczema on the penis .....	9 cases	
"      "      and suppuration on the penis ..	1 "	
Dysuria .....	14 "	
Pain in testes .....	2 "	
"      "      penis .....	1 "	27 cases
	Total	265 cases
		(= 79.3 %)

## URETHRITIS

Urethritis occurred in 238 cases, or 71 per cent, and in 89.8 per cent of all cases of urogenital involvement. Its subjective symptoms were usually urethral itching and burning which increased during and after urination; occasionally increased frequency was also observed. The discharge was not generally so abundant as in gonorrhœal urethritis, but occurred chiefly on pressure of the urethra. In most cases it was thin and greyish, more rarely thick and purulent. On microscopical examination the discharge showed numerous leucocytes but no bacteria, or only such as are commonly present in the urethra. Cultures were negative for gonococci (Cf. p. 99). Unfortunately no differential leucocyte count was made from the urethral pus or the muco-purulent ocular discharge. An eosinophil cell count was made from a urethral speci-

men once in each of 25 cases. The result was as follows: in 12 cases 0 per cent, in four cases 1—4 per cent, in four cases 6—10 per cent, and in five patients 17—57 per cent. The other cells were chiefly neutrophils. — The degree of smarting varied greatly from case to case. Sometimes it was very severe and caused much discomfort, sometimes it was very mild, or even entirely absent; in that case the patient only observed the urethral discharge, or even that escaped his notice and it was noted only on examination. In 24 cases the margins of the urethral meatus and the adjacent parts were reddened, occasionally pouting of the swollen urethral mucosa was observed. The duration of the urethritis varied greatly, as did the intensity of its symptoms. In some cases it seemed to clear in one day, in others it lasted for several months. The great majority (87 per cent) of the cases recovered in one to four weeks, about one-half of the cases as early as during the first week (*Cf.* p. 77). In all prolonged cases a marked undulation was observed in the severity of the symptoms.

#### CYSTITIS

Symptoms from the bladder were present in 22 cases; in 10 of these urethritis could not be clinically recognized. The diagnosis of cystitis was based chiefly on the clinical symptoms: frequency of urination amounting to 30—50 times daily, pain and tenderness on pressure in the floor of the pelvis. We had no opportunity of performing cystoscopic examinations while these symptoms were still present. Only later — when the clinical bladder symptoms had already vanished — 17 patients were submitted to cystoscopy by the urologist (Aulis Korhonen, M.D.). Some of these patients had had bladder symptoms, but some only urethritis and penile erosions. It was noted that in nine patients the region of the *trigonum vesicæ* was more or less reddened, the mucous membrane of the bladder appearing normal elsewhere. In eight patients the cystoscopic findings were quite normal. In each of the 17 cases a urine specimen was taken from the bladder in connection with cystoscopy. All specimens were clear and free from albumin. The sediment showed very few leucocytes. Stains (Löffler and Gram) and cultures (Conradi-Drigalski's agar and

blood agar) were negative for bacteria (*Cf.* p. 99). — In one patient who had very severe bladder symptoms but was not cystoscoped the initial and last part of the spontaneously passed urine was turbid and contained a great number of greyish lumps and floccules which did not disappear on boiling or adding nitric acid and resembled an amorphous mass under the microscope. The sediment also showed numerous leucocytes and varying numbers of erythrocytes, but no casts. In one case there was gross terminal hæmaturia, and the urine later contained visible blood floccules for some days. Stains, cultures, and dark field examinations were negative. Mild bladder symptoms were accompanied by a hæmaturia lasting for one to three days in three other cases; no casts were found and the urine was sterile. The duration of the bladder symptoms generally varied from a few days to two or three weeks. However, in one instance they occurred at irregular intervals over a period of five months, and in the case described above over nine months (*Cf.* p. 78).

#### NEPHROPATHIES

In six cases some albuminuria was noted, the 1—3 specimens obtained at intervals of two to six days being slightly positive (boiling test). In one case the amount of albumin was  $\frac{3}{4}$  per mille (Esbach). These reactions later became negative. The sediment showed an increased leucocyte count, either alone or together with erythrocytes, epithelial cells, and a few hyaline and granular casts. The urine was sterile, acid. The blood pressure was normal.

In the case described above with severe bladder symptoms albuminuria appeared two months after these symptoms and lasted for nearly two months; the highest amount of albumin was 3.4 per mille.

The daily output of urine varied from 1,040 to 2,900 c.c., being generally below 2,000 c.c. The specific gravity measured 1.007—1.015. The urinary sediment now showed a large number of leucocytes, but little or no erythrocytes, except in two tests in which the latter were numerous. There were no casts. Stains and cultures were negative for any pathogenic organisms. The patient had no headache and no noticeable œdemas. The

pulse was even and regular, rate about 60 to 80 per minute. In repeated measurements the blood pressure was normal or subnormal (100/50 mm. Hg). Auscultation, X-ray, and electrocardiographic examination of the heart revealed no pathology. The number of white blood cells, which had earlier been 7,000, rose to 13,700 when nephropathy set in, and the differential count showed a "shift to the left" and monocytosis. The sedimentation rate of the blood which had fallen to 26 mm. from 53 mm. at the onset of the disease, rose again to 73 mm. The total blood cholesterol was 190 mg per cent, the blood potassium 20.9 mg per cent, and the calcium 10.3 mg per cent. Vitamin studies gave the following results. In the blood: vitamin C 0.85 mg per cent, vitamin A 112 I.U./100 c.c., carotene 22.0  $\gamma$  per cent, nicotinic acid 1.20 mg per cent. In the urine: vitamin B<sub>1</sub> 112.7  $\gamma$ /24-hour urine. Henry's and Takata's tests were negative. The patient had no fever, except for a few slight elevations of temperature.

In another case nephritis developed in addition to bladder symptoms and articular swelling. The case is reported below:

A private, aged 29. Family history non-contributory. As a child the patient had had some kind of inflammation of the eye, but he did not know the exact nature of the disease. On some occasion earlier he had been troubled by slight diarrhoea, and now for two years occasionally by dyspepsia. In 1943 he had suffered from low back pain. Urination was not painful at that time.

On August 24, 1944, while at the front, he contracted a mild dysentery which lasted for seven days. Symptoms of fever were present for two days and bloody diarrhoea for three days. Table 9 shows the patient's symptoms and their duration. Besides the urethritis and cystitis a sharply margined erythematous skin lesion appeared around the urethral meatus, on the glans and the prepuce. Hypospadias was noted: the opening of the urethra was in the region of the frenulum. September 20. Cystoscopy (Aulis Korhonen, M.D.): The capacity of the bladder was 300 c.c. There was a fairly marked redness in the area of the trigonum and also around the ureteral orifices, especially the left. Elsewhere the mucous membrane appeared normal, erosions or ulceration were not observed. From both ureters an ordinary urinary stream escaped at regular intervals. A urine specimen obtained from the bladder on the same occasion showed no pathological findings and culture yielded no growth. Also on November 18 the urine specimen from the bladder was clear, free from albumin, cells, and bacteria. On December 2, 1944, the patient felt a pain in the sacral area and urgency of urination. He had to empty his bladder more than ten times during the night. A urine specimen obtained by catheter was yellow, rather turbid and alkaline, with an albumin content of 0.5 per mille. Numerous red blood cells, a few epithelial cells, but no casts, were



A mild and temporary albuminuria present in the six cases reported above might be interpreted as a symptomatic nephrosis accompanying infectious diseases. Four of these patients also had fever — 38.1 to 38.8°C. — at the same time, but two had a normal temperature.

There was also one case in which the albumin in the urine amounted to 3/4 per mille. The sediment contained leucocytes and erythrocytes, a few epithelial cells, and hyaline and granular casts. As there was also burning on urination, urethral discharge, and tenderness to percussion in the area of the right kidney, the assumption appears justified that the urethritis had been complicated by a renal disease resembling pyelonephritis and due to the same cause as the urethritis. In another case the picture also resembled pyelonephritis (Cf. p. 56); two months after the onset of urethritis and cystitis a renal disease was superadded and lasted about two months.

The ætiology of the case of nephritis reported on p. 57 seems more complicated than that of the nephropathies described above; at the onset of the renal symptoms gram-positive diplococci were found in the urine. Some circumstances indicate, however, that in this case also the renal disease might have the same ætiology as Reiter's disease, and that the bacteriological finding would be of no ætiological importance. First, a cystoscopic examination before the renal symptoms had started revealed marked signs of inflammation in the bladder; on the same occasion the urine was free from organisms. Consequently, some factor other than the diplococcus seems responsible for the urinary tract becoming involved. Second, the diplococci disappeared from the urine after sulphonamide therapy and were not observed later, but the patient had the same rise of temperature during that therapy and afterwards. The renal symptoms occurred only intermittently during the first 2 ½ months, and it is thus uncertain whether even their first disappearance can be ascribed to the sulphonamide treatment, or whether it was spontaneous as were the later ones. The patient's articular symptoms did not at this time any longer account for the fever. On the other hand, a coincidence was observed a few times between the increase of the pathological

findings in the urine and the rise in temperature. Thirdly, it is possible that the nephritis might have been caused by the p-aminobenzolsulphonamide (total dose 52 g.), but the fact that pyelonephritis was noted already before administration of this drug is in opposition to this hypothesis.

*It thus appears that nephropathies resembling symptomatic nephroses, pyelonephritis, and nephritis may also occur as symptoms of Reiter's disease.*

#### PENILE SKIN LESIONS

Apart from a reddening of the urethral orifice and adjacent parts the series includes 87 cases with penile eruptions (equalling 32.9 per cent of the cases with urinary involvement and 26.1 per cent of the total number of cases). Ten of these patients had showed no symptoms or signs of urethritis, but the rest had had urethritis. The dermal lesion appeared most frequently and was marked in the region of the frenulum and around the urethral meatus, but also elsewhere on the glans and the prepuce. It consisted of reddish or greyish patches, 2 to 3 mm. — more rarely 5 to 10 mm. — in diameter which were sharply margined, raised from their base, and round or oval in shape. Occasionally there was a pit in the middle of the patch and the border was raised. Sometimes the lesions were coalescent and serpiginous figures thus developed. In most cases the lesions were dry and covered in places by a thin yellow brown crust; occasionally they also suppurated or there were superficial ulcerations which were, however, presumably due to secondary infection probably partly accounted for by poor penile hygiene.

This skin eruption caused the patient no appreciable discomfort and often it was noticed only by chance. It gradually disappeared, the duration varying from one week to seven months (Cf. p. 78).

Penile lesions were more frequently observed in this series than in earlier reports. They are generally not mentioned in those dealing with more extensive material, but in smaller series a few cases with penile lesions are described. However, in recent investigations where the cases have been more closely observed

such lesions have been more frequent (Cf. p. 23). This difference may be partly due to the fact that a skin lesion of this kind often appears later than the urethritis and is thus easily overlooked. Penile lesions seem to occur also in the absence of urethritis and thus they should be regarded as a symptom of Reiter's disease and not as a consequence of it.

#### INVOLVEMENT OF TESTES AND EPIDIDYMISS

Pain and tenderness in one or both testes without noticeable swelling or changes in consistency occurred in only six patients of the whole series; in two of these it was the only symptom in the urogenital system. The pain and tenderness lasted for a few days in all except one case which had a duration of four weeks. In addition to these six patients there were three who developed a unilateral orchitis and epididymitis resulting in swelling and hardening, one with a bilateral epididymitis, and one with a unilateral orchitis. Three of the patients just mentioned had initially suffered from urethral discharge or the passing of urine had been difficult. Simultaneously with the pain on urination, or after it had disappeared, pain and tenderness in the sex glands set in and they became swollen. In one patient bilateral epididymitis developed as late as 22 months after the urinary symptoms. In the cases of orchitis the testis was enlarged throughout, definitely firmer than usual, but not particularly hard, and showed a fairly marked pressure tenderness. The epididymis, on the other hand, was only once enlarged throughout; it was of the thickness of a thumb, hard and tender. In the other cases the process appeared localized rather to the caput of the epididymis, and once the cauda seemed to be involved in addition. The nodes present in these cases were about the size of a finger tip, initially hard and tender, later soft and only slightly tender. The duration of the symptoms of orchitis varied from one week to two months, but those of epididymitis lasted longer. In three cases there were still distinctly recognizable, but no longer tender nodes in the cauda of the epididymis when the patients were discharged after being treated for three, four, and five months respectively. In

one case one epididymis became asymptomatic in four, the other in nine months (Cf. p. 78).

## PLEURISY

Dry and circumscribed pleurisy was definitely diagnosed in 26 cases (= 7.8 per cent). This diagnosis seemed very probable in 48 other patients. Thus with reasonable certainty the disease involved the pleura in 74 cases (= 22.2 per cent). The pleurisy was unilateral in 60 cases and bilateral in 14.

All cases of pleurisy were very mild in character and showed but few subjective and objective changes. Exudation was noted in none of the cases. In 23 instances the diagnosis was based on fluoroscopic changes which had appeared during the course of treatment. Besides these changes about one-half of the cases experienced a stitch or pain in the side when breathing or showed auscultatory changes (pleural friction), or both. In three cases no changes were observed on fluoroscopy which was carried out once, but in each of them there were subjective complaints and decidedly positive findings on auscultation.

Röntgenological examination of the chest was made in 321 cases, altogether 718 times, and changes of the pleura were noted in a total of 86 patients. In 23 of these cases active changes were observed and in 63 one or both pleural sinuses were adherent. As only 15 of the latter group had reported a previous pleurisy or pneumonia, it appears more than probable that at least in some of these patients, perhaps even 48, the pleurisy may have been caused by Reiter's disease. X-ray examination did not, however, reveal this definitely, as — contrary to the 23 cases mentioned above — no active changes in the pleura could be demonstrated. True, 38 of these cases were subjected to fluoroscopic examination only once, but 19 patients twice and 6 three times. That the pleuritis was active is, however, supported by the fact that of the 48 patients 13 showed also other subjective or objective signs: seven had a stitch in the chest or pain in the back, three pericarditis, and three auscultatory changes suggestive of pleuritis.

The series differs from those of others in that the incidence of

pleuritis was higher and there were no exudative forms. It appears that, to recognize pleuritis in connection with Reiter's disease, repeated roentgenological examination as well as frequent — preferably daily — auscultation is of great importance.

## CARDITIS

The chief measures used for demonstrating heart complications were auscultation, and electrocardiographic and roentgenological examination. The shortage of films due to war conditions necessitated a reduction of the number of electrocardiographic examinations and prevented the use of the chest lead. For the same reason roentgenograms could be made in only part of the cases.

Auscultation of the heart was frequent, in most cases daily, especially during the period of fever. This chiefly aided the study of the variations in the quality and intensity of the heart sounds, and of murmurs and pericardial friction sounds. Electrocardiographic examination was made on 308 patients, the number of electrocardiograms was 837. The number of patients submitted to X-ray examination was 321, the roentgenograms numbering 253 and the fluoroscopic examinations 466. These revealed permanent pathological changes of the heart in four patients; however, on the basis of the history and the clinical course they seemed to be due to myocardial disease caused by previous myocarditis. In 23 patients the findings justified the diagnosis of carditis.

These 23 cases comprised four showing symptoms of both myocarditis and pericarditis, 16 of only myocarditis and three of only pericarditis. On the other hand, involvement of the endocardium could not be definitely demonstrated in any.

There were electrocardiographic alterations in 20 cases. The electrocardiograms of one of these patients have unfortunately been lost; in the others the following changes were observed:

In nine cases the PQ-interval was prolonged; it was either normal at first and later prolonged, or prolonged in the first electrocardiogram, becoming later normal. The PQ-interval was

considered prolonged when it was 0.21 or more; the maximum was 0.38 second. Besides a prolongation of the PQ-interval other abnormalities were observed in all nine cases, for instance widening of the QRS-complex (0.11—0.12 sec.), elevation of the ST-segments, and changes of the T-waves, or combinations of these alterations (a positive T-wave became very low or isoelectric, biphasic, or negative in Leads 1 and 2 in all three leads). It should be added that the PQ-distance was not reduced in exercise tests of two cases, on the contrary it was slightly prolonged, and there was fusion of the P- and T-waves.

In nine cases the PQ-interval was normal but pathological changes were observed in the T-wave: it became isoelectric, biphasic, or negative. These changes occurred in six patients in all three leads, in two in Leads 2 and 3, and in one case only in Lead 3. Even the last of these cases can be regarded as carditis, as besides the variations in  $T_3$  — it was twice biphasic and once negative — a widening of the QRS-complex was noted in Lead 2 (0.11 sec.) and in Lead 3 (0.13 sec.), and a slightly elevated ST-segment in Lead 2 and 3. A pericardial rub was heard at the same time. This group of nine patients included four who showed — besides the abnormal T-wave — widening of the QRS-complex (0.11—0.13 sec.) during the course of the disease, elevation of the ST-segment, or both.

In one case the PQ-interval and the T-wave were normal, but the  $QRS_1$  and  $QRS_3$  were widened (0.11 and 0.13 sec.), and the ST-segment was elevated in Leads 1 and 2; ventricular extrasystoles also occurred. Further, in one case the diagnosis of myocarditis was based on electrocardiographic alterations and auscultation, but the electrocardiograms have been lost.

The diagnosis of pericarditis was, in seven cases in which it appeared certain, based on auscultatory and electrocardiographic findings. In three cases there was a pericardial friction sound; in two of these also elevation of the ST-segment in Leads 2 and 3 and in one only in Lead 1. In four other cases the ST-segment was normal, but a pericardial rub was audible in each case. The seven cases of pericarditis included three in which involvement of the myocardium could not be demonstrated, but in the rest

myocardial affection was diagnosed, as described earlier. In addition to these seven cases, the present series included six in which the diagnosis of pericarditis was probable. In four of these there was — besides myocarditis — an elevation of the ST-segment (in three patients in Leads 1 and 2, in one in Leads 2 and 3), and in two probably a pericardial friction sound; of the latter two, one had a normal electrocardiogram while the other indicated myocardial injury.

X-ray examination of the heart was made in 22 cases one to four times during the carditis, and in two cases before carditis was diagnosed. These studies revealed no pathology.

On auscultation pathological changes were found in 16 patients. Thus the heart sounds were diminished, even almost inaudible, in eight cases, and in one they were exaggerated. A pericardial rub was noted in seven cases; in three of these it was the only abnormal finding on auscultation. In three cases it was accompanied by a systolic murmur, and in one case by a diminution of the heart sounds. In two other cases, besides these seven, there was in all probability a pericardial rub and a systolic murmur at the pulmonary area. A systolic murmur was found in 11 cases in eight of which it either appeared or disappeared during the treatment. A diastolic murmur was not observed in a single case.

Slight fever occurred at times during the carditis in about half of the patients. Seven had a rise of temperature only for one to two weeks and five for a longer period, the maximum being eight weeks. The pulse rate usually corresponded to the temperature of the patient. In five cases, however, the pulse rate was rapid (c. 100 to 110 per minute), although the temperature was normal.

The sedimentation rate was generally markedly increased in the cases of carditis. It was normal in only 3 patients. As all the patients with heart involvement had also arthritis, it is difficult to judge definitely the role of either in the fever and the sedimentation rate.

There were subjective cardiac symptoms — pain in the precordium — in only four cases. In all of these a pericardial rub was also heard.

The exact time of onset and duration of the carditis is not distinctly revealed by the material, as more frequent electrocardiographic examinations could not be made (Cf. p. 63). However, in six cases the first electrocardiogram — taken 7 to 28 days after the onset of Reiter's disease — was normal, but the next tracing — 20 to 59 days after the onset — showed pathological alterations. Yet in 14 cases there were abnormalities even in the first tracing 6 to 60 days after the disease began. In one case the pericarditis started as late as 32 months after the onset; the patient still had slight articular symptoms at that time. Accordingly, it can be said that a carditis caused by Reiter's disease may occur as early as during the first week of the disease, but may also start later, even after two or three years. On the basis of clinical and electrocardiographic observations the duration of the carditis seems to vary from 1 ½ to 5 ½ months. At the end of the treatment four patients still showed slight electrocardiographic abnormalities, but as no after-examinations were carried out, it is not possible to say whether they were permanent or not.

#### OTHER LESIONS

Except for penile involvement (Cf. p. 60) there were comparatively few cases of skin lesions. Herpes labialis occurred in five cases and in one patient herpetiform vesicles appeared at the base of the nose; urticaria occurred in two patients. Twenty-nine patients had acute rhinitis at the initial stage, but only one had epistaxis; in this respect the series differs for instance from Gounelle's cases (Cf. p. 22). The specific nature of these symptoms in Reiter's disease cannot be decided on the basis of this series, because in view of the war conditions it seems that 29 cases of rhinitis in a group of 334 individuals must be looked upon as "normal". The same applies to the epistaxis, herpes, and urticaria.

During the treatment two patients developed rupia on the arms, trunk, and thighs; it healed well with the ordinary treatment and seemed to be identical with the hyperkeratotic lesions described earlier (Cf. p. 24).

Stomatitis occurred in nine patients. On the palate and the mucous membrane of the lips and cheeks there were greyish or reddish erythematous patches, slightly raised from their base, and about 2 mm. to 1 cm. in diameter. In addition, macular hæmatomas were sometimes present in other parts of the oral mucosa. No deep ulcerations of the mucous membrane were observed. Only some points of the mucosa were reddened, but it seemed that the process was entirely superficial in these cases too. *Fætor ex ore* or gingivitis did not occur. No pathological changes were noted in the teeth, with the exception of caries in four patients. The mucosal lesions were tender and caused discomfort especially when eating. Their duration varied from a few days to five weeks. Considering the high incidence of different kinds of stomatitis under war time conditions, it is difficult to draw any conclusions as to the specific nature of the oral mucosal lesions. However, it seemed that they differed in clinical manifestations from other war-time cases of stomatitis, which most frequently occurred in association with gingivitis and were aphthous or ulcerating and foul-smelling.

Bilateral mastitis developed in a man of 37 three months after the onset of the syndrome and while articular manifestations were still present. The patient experienced slight pain in both mammary glands where, in the region of the areola, a round, very firm and tender formation with a nodular surface and 2 cm. in diameter, could be palpated. The *areola mammæ* over it moved freely, and on pressure a small amount of colourless clear fluid escaped from the mamilla. The inflammation gradually disappeared without any special treatment, in the course of four months. This was evidently a specific, although rare, symptom of Reiter's disease which Sick (1918) has earlier described in two cases.

No symptoms were observed in the central and peripheral nervous system in the present series which in this respect differs from some previous ones (Cf. p. 20).

As regards the abdominal organs only four patients complained of dyspeptic symptoms. Two of these had achylia and one hypochylia. Röntgenological examination of the ventricle

in these cases showed normal conditions. A test meal (c. 30 g. wheat rusks or bread, 250 g. water, withdrawn after half an hour) was given to 287 patients and the results correspond roughly to those normally obtained in Finland. In none of the cases could enlargement of the spleen or liver be demonstrated and the abdominal organs also showed no other pathological changes; thus the findings in this respect agreed with several earlier studies (*Cf.* p. 22).

The urine of 305 patients was tested once or several times (maximum 5) at weekly intervals for bilirubin, for urobilinogen, and for urobilin; the tests were negative in all except 12 cases in which the urine contained urobilin and urobilinogen. As this appeared during the fever phase — and especially in view of the small number of cases — it seems that no particular importance can be attached to this fact.

## FEVER

The fever of the patients was measured in the axilla. The morning temperature was taken immediately on waking and the evening temperature at about 4 p.m. before dinner, only exceptionally later in the evening.

The incidence of fever in this series corresponds roughly with earlier results, as does the height and duration of fever (*Cf.* p. 25). Table 10 shows the highest axillary temperature in the 320 cases where no other cause of fever could be demonstrated during the period of observation.

TABLE 10  
BODY TEMPERATURE

	Maximum temperature (°C., axilla)			
	— 37	37,1—38	38,1—39	39,1—40,2
No. of cases .....	60	118	99	43
Per cent .....	18.7	36.9	31	13.4

60 cases = 18.7 %    260 cases = 81.3 %

The cases with an axillary temperature of over 37°C. are considered as having fever. In the 258 febrile cases where it was possible to get the information required, the duration of fever

varied from one day to more than six months, which is shown in detail in Tables 11 and 12.

TABLE 11  
DURATION OF FEVER

	Duration of fever, weeks												
	0—1	2	3	4	5	6	7	8	9	10	12	14	26
No. of cases .....	135	36	28	15	10	10	9	4	6	2	1	1	1
Per cent. ....	52.3	13.9	10.8										
<hr/>													
	199 = 77 %												

Total 258

In Table 11 the figure under the heading "duration of fever" denotes that the fever stopped during that particular week of the disease, and Table 12 again shows how many days the fever lasted in the cases in which it stopped during the first week.

TABLE 12  
DURATION OF FEVER IN THE CASES IN WHICH IT SUBSIDED DURING  
THE FIRST WEEK

	Duration of fever, days						
	1	2	3	4	5	6	7
No. of cases .....	32	30	22	8	9	8	26
Total 135 cases							

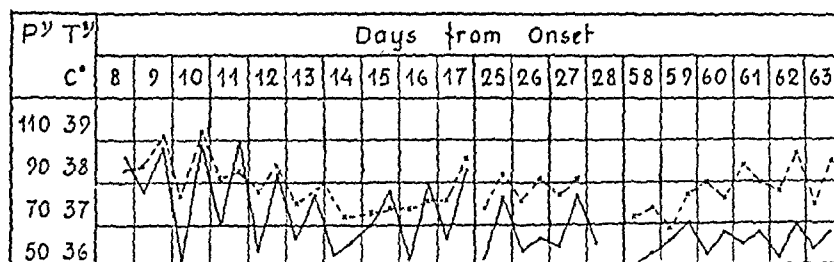
Generally the fever started gradually without actual chills; some patients, however, had a feeling of chill. No special type of fever characteristic of Reiter's disease was observed, but it was usual that the patient had no fever or was subfebrile in the morning, the temperature rising in the afternoon. The difference between the morning and evening temperature was thus generally great, even  $2\frac{1}{2}^{\circ}\text{C}$ . In one and the same patient the fever could be continuous and then vary indefinitely with large remissions, being even sometimes absent for days. No steep fall of temperature was observed; the fever decreased gradually, and especially in the cases in which it lasted for several weeks, there occurred at the terminal stage short, slight or marked elevations of tem-

perature of one or two days' duration at irregular intervals. In the cases where the fever lasted only one to two days it was never high. — The form of the pulse curve was roughly similar to that of the fever curve.

Definite sweating was observed in 68 patients (=20.4 per cent), but it was not very severe and occurred chiefly at the early stage of the arthritis during one or two weeks.

In Tables 13, 14, 15 and 16 some typical fever and pulse curves are given, each table showing different periods of the same patient's fever. In the diagram the morning and evening temperature are marked for each day of the disease, the days being numbered from the onset (Pulse, broken line).

TABLE 13



<sup>1</sup> P = Pulse rate.

<sup>2</sup> T = Temperature.

TABLE 14

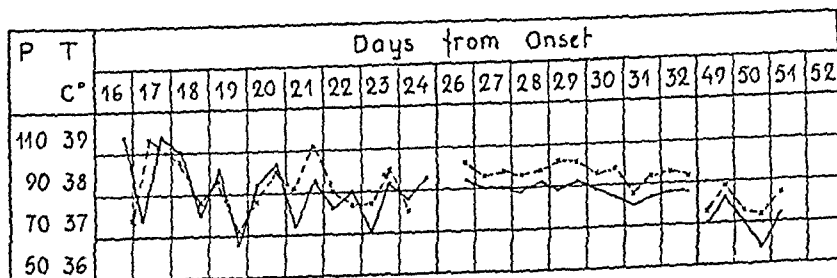
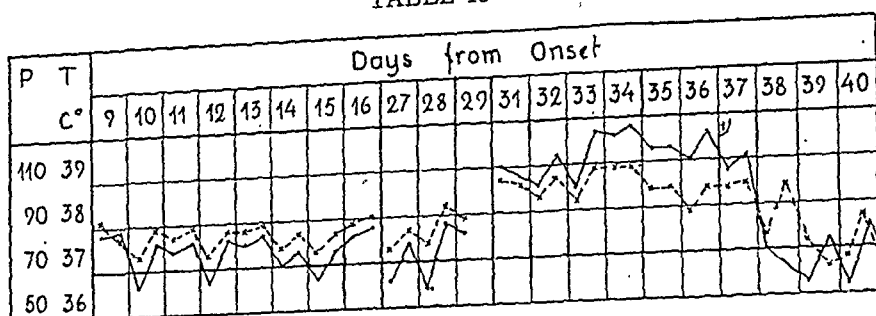
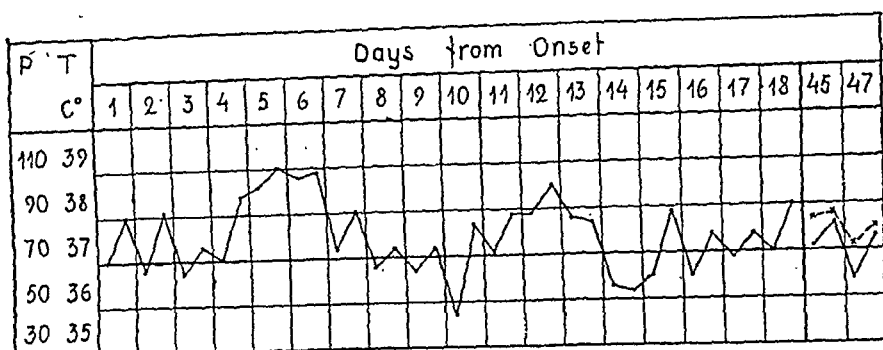


TABLE 15



Pyramidon 0.6×3 daily.

TABLE 16



### SEDIMENTATION RATE

The sedimentation rate in one hour was determined by the Westergren method in all the cases. The test was first made once a week and later — when the sedimentation rate was already normal — at less frequent intervals. All cases where variations in the sedimentation rate could be attributed to some cause other than Reiter's disease (Cf. p. 79, concurrent diseases) were omitted. Some cases, again, were omitted because the sedimentation rate was tested too seldom after the patients were allowed to have treatment at home. Among the 319 patients thus examined 26 had a normal sedimentation rate (2—10); in the others it was increased, the maximum being 11 to 50 in 103 patients, 51 to 100 in 99, and 101 to 143 mm. in one hour in 91 patients. This sedimentation rate was noted in 230 cases of 279 (82.4 per cent) dur-

ing the first month of the disease, but elevations occurred even three months after the onset. The increased sedimentation rate returned to normal in 37 patients of 200 during the first, in 140 during the second to the fourth month, and in the rest later, the maximum being 13 months.

In five cases accompanied by articular swelling or exudation in the joint cavity the sedimentation rate was normal during the whole course of the disease, and in 14 cases it was only slightly increased, between 11 and 20 mm. On the other hand, sedimentation rates up to 75 mm. were observed even in cases with only subjective articular findings. Twenty-one out of 59 such cases of arthralgia showed a normal sedimentation rate, but in the rest it was more or less increased. — At the termination of the treatment 42 patients had a sedimentation rate above 10 mm.; in 26 cases it was 11 to 15 mm., in nine 16 to 20 mm., in five 21 to 25 mm., and in one 33 mm. after barely four months' treatment, and in one instance 64 mm. as late as after more than a year. These last two patients insisted on being discharged, although their treatment was still incomplete. Except for a slight increase in the sedimentation rate — the rest of the 42 patients were either entirely asymptomatic when they were sent home, or had such mild symptoms that discharge was considered possible. These patients were requested to return if the symptoms recurred or were exacerbated. In most of the cases the sedimentation rate became normal while other symptoms were still present. Cases with swollen joints and even a large amount of exudate in the joint cavity were observed after the sedimentation rate had been normal for many months.

Of the three cardinal symptoms the articular affections seemed to cause the most marked changes in the sedimentation rate. The eye symptoms, on the other hand, were accompanied by a normal or only slightly increased sedimentation rate. However, in two cases with eye symptoms it was markedly increased (68 and 70 mm.). In the cases of orchitis and epididymitis the sedimentation was also normal or only slightly accelerated. The relation between the sedimentation rate and the heart complications has been described already (p. 65).

In a few cases of pleurisy the sedimentation rate was normal. In the majority, however, it was increased but the joints were then also affected, as in the cases of carditis.

The sedimentation rates in this series agree in the main with previous investigations (Cf. p. 26) which, however, do not mention the relation of the sedimentation rate to the different symptoms; thus a comparison on this point is impossible.

#### OTHER BLOOD STUDIES

The following vitamin determinations were carried out in five cases. From the blood: Vitamin A and C, carotene, and nicotinic acid. From urine: Vitamin B<sub>1</sub>. In the same cases the blood calcium and potassium, total cholesterol and non-protein nitrogen were determined, in one instance also the blood urea. The Takata-Ara test was made in three cases and Henry's test in four. The result in all these tests were normal, except for one case, in which Henry's test was first positive, but 17 days later negative.

#### BLOOD PICTURE

The hæmoglobin was determined and the red and white cell count made on 302 patients repeatedly (generally 3 or 4 times, maximum 12) at intervals of one to two weeks in the initial stage of the disease and later only if the clinical findings seemed to require it. In most (3/4) of the cases the first examination was made in the second to fourth week of the disease, in less than 1/4 of the cases during the second month, and only in some instances during the first week (12 cases) or the third and fourth month (7 cases).

It was found that the hæmoglobin (Sahli) in 20 cases ranged from 52 to 60, in 70 (=23.1 per cent) from 61 to 70, and in all others (=70.3 per cent) it was higher, the maximum reaching 100. The red cell count varied as follows: in two cases from 2.9 to 3.0 mill./cu.mm., in 25 from 3.1 to 3.5 mill., in 68 from 3.6 to 4.0 mill., and in the remaining cases (=68.5 per cent) the number of red blood cells was higher, with a maximum of 5.5 mill. If a hæmoglobin of 52 to 70 (Sahli) and an erythrocyte count of 2.9 to 4

mill. are regarded as anæmia, 116 patients (38.4 per cent) were anæmic at the first examination. In 80 of the patients both the hæmoglobin and the red cell count were reduced, in 21 only the hæmoglobin, and in 15 only the number of erythrocytes. In most cases the anæmia was normochromic, including the last-mentioned 15 cases, and only a small proportion was hypochromic. In addition, a mild hyperchromic anæmia was noted in three cases, but a more detailed investigation revealed bothriocephalus anæmia. This series does not clearly show whether the anæmia is a specific symptom of Reiter's disease. It may also be ascribed to the stress of war and the monotonous diet, but in opposition to this is the fact that most patients had had Reiter's disease for two to eight weeks before the blood count was made — there being thus time for anæmia to develop — and that anæmia was observed to set in in 12 cases during hospitalization. Accordingly, the anæmia occurring in Reiter's disease seems to be of the same type as seen in infectious diseases in general.

When these 12 cases are included it appears that anæmia was present in 128 cases, or c. 42 per cent. As previous reports have contained few statements on the red cell count and as it, according to them, has shown no pathological changes, except that Twiss and Douglas (1946) noted secondary anæmia in two cases and Storm-Mathisen (1945) in one case (*Cf.* p. 26), the present study should throw added light on the subject.

A study of the white blood cells revealed that the white cell count varied in 2/3 of the cases from 4,000 to 8,000. In about 1/4 of the cases it was above 8,000, ranging in 48 patients (=15.8 per cent) from 10,000 to 18,000. White cell counts under 4,000 were observed in 18 cases, the lowest figure being 3,000. A differential count showed a "shift to the left" in 64 cases (21 per cent), the percentage of neutrophil rods being 6 to 20.5. Juvenile forms were found in only two cases and then not more than 0.5 per cent. Eosinophilia (5 to 11.5 per cent) occurred in 100 patients (=33 per cent). In 41 cases (13.5 per cent) the number of monocytes was increased (10—21.5 per cent), and in 18 cases the lymphocyte count varied from 40 to 56 per cent. A thrombocyte count was made in only 13 cases; their number varied from 92,000

to 498,000. The leucocytosis seemed to be due chiefly to an increase of the neutrophil cells, and it occurred most frequently (in more than  $1/2$  of the cases) during the first month of disease and later more rarely. The incidence of the "shift to the left" and of monocytosis was also highest during the first month;  $2/3$  of the former and  $3/4$  of the latter cases were noted at that time. Eosinophilia was observed in  $1/3$  of the cases during the first, in  $1/2$  of the cases during the second month, and in the rest later. The blood picture in the present series agrees in the main with that described in earlier investigations (Cf. p. 26), even if it is not possible to compare the incidence of various pathological findings with previous reports as the latter lack the required data.

## DURATION OF REITER'S DISEASE

### a) ARTHRITIS

In all 313 cases ( $\approx 93.8$  per cent) in which the arthritis was accompanied by other symptoms, the former invariably persisted after the other symptoms had vanished. Seeing that articular affections were in 43 per cent of the cases the single initial symptom of the syndrome, or a part of the initial symptom complex, and that all the cardinal symptoms in 85 per cent of the cases (Table 3, p. 44) began between the first and twentieth day of the disease, it can be said that the duration of the arthritis in this series corresponds fairly closely to that of the whole disease.

The duration is not known in 23 cases of 325, owing to the patients being transferred to other hospitals or to the clinical reports lacking definite final data. In any case the disease had lasted for some months in 20 of the patients mentioned and over one year in three patients. It is noteworthy that none of the cases with marked articular swelling recovered during the first month; the recovery began at the earliest in the second month. Of these cases 53 per cent recovered during the second to fourth month, and four patients were ill for more than one year, the longest duration being 16 months. In the cases of arthralgia, on the other hand, recovery was observed already in the second week; 24 per

cent recovered during the first month, 90.7 per cent during the first three months, the longest duration being about eight months, in one case. If all cases where the joints were involved are included, 240 cases (79.4 per cent) recovered completely; of these 205 cases (=67.7 per cent) recovered during the first five months, the incidence of recovery being highest (45 per cent) during the third and fourth months.

In addition to the cases described above resulting in complete recovery there were 62 patients (20.6 per cent) who, at the end of the period of observation, still showed a small amount of synovial exudate, slight swelling, minimal deficiency of extension or flexion, or crepitation felt on manual palpation and plainly heard at the distance of several metres. Four patients showed also marked muscular atrophy after 6, 8, 15 and 16 months' treatment. Generally these symptoms were mild and caused the patients no appreciable discomfort, except before and during bad weather.

The longest time of observation was three years; at its end the patient still had some fluid in one knee and definite crepitation in both knees. His joints moved freely and were tender only on strenuous exertion and in bad weather. After being treated at hospital and at home for 1 ½ years the patient had been doing agricultural work and during this time slow, but continuous improvement of the joint symptoms had been observed. The sedimentation rate, which was high at the onset, became normal in four months.

The greater part of the articular symptoms thus seemed to disappear in a few months, but in some cases the course was protracted and symptoms observed as late as after one to three years of treatment. Why the disease was thus protracted is not revealed in the present material. These cases had begun and were treated under similar conditions as those that recovered more rapidly. The history and examination gave no clues as to previous or concurrent diseases which might have affected the course of the illness. However, one patient whose disease had lasted 17 months and who then still showed slight articular swelling and a slightly elevated sedimentation rate, had earlier had gonorrhœal arthritis. Another patient with some fluid persisting in the knee joint but

a normal sedimentation rate after 15 months' treatment, had had an acute polyarthritis twenty years earlier. In these cases the previous joint disease may have contributed to the slow recovery, although this does not seem usually to be the case, as in 23 other cases with a previous acute arthritis a prolonged course was not observed. As regards the persistent symptoms analyzed on page 76 the presence of joint exudation definitely shows that recovery is not yet complete, although the sedimentation rate is already normal (2 to 9 mm.). The same can be said of the group with slight articular swelling. Of these cases, too, one-half had a normal sedimentation rate, and in the other half it was slightly increased (12 to 33 mm.). In the group showing crepitation only four patients had a slightly increased sedimentation rate (13 to 25 mm.), while the others (31 patients) had normal sedimentation rates. As it had appeared that the condition of the patients who were given convalescent leave had continually improved during that time, and there had even been complete recoveries, such patients were discharged at their own request after two to five months, in spite of the symptoms described above.

#### b) OCULAR MANIFESTATIONS

The duration of the ocular manifestations was in each case shorter than that of the arthritis. The duration of the conjunctivitis (268 cases) varied from two days to seven months; slightly less than 4/5 recovered in one to four weeks. Reddening of the conjunctivæ without other ocular changes could last for one month at a stretch, but in cases of conjunctivitis of several months' duration it was usually very mild with temporary exacerbations. Iritis (17 cases), keratitis (17 cases), and kerato-iritis (7 cases) recovered within one to five months.

#### c) UROGENITAL INVOLVEMENT

The affections of the urogenital system disappeared before the arthritis, as did the ocular manifestations. The duration of urethritis (202 cases) varied from one day to nine months; 87 per cent recovered in one to four weeks. It should be mentioned

further that in numerous cases (34 cases=16.8 per cent) the duration of urethritis was only one or two days and that in all cases with a longer duration (of several weeks) the severity of the symptoms undulated as in the cases of conjunctivitis. The duration of cystitis (22 cases) varied from one week to nine months, that of orchitis (10 cases) from one week to two months, and that of epididymitis (four cases) from three to nine months; the penile eczema (72 cases) lasted from one week to seven months. In three cases of epididymitis small nodes still remained when the treatment had lasted for three to five months.

As regards the duration of Reiter's disease the present series agrees fairly well with previous reports.

### RECURRENCES

No follow-up studies were carried out with a view to discovering recurrences, but the army patients were notified on termination of the treatment that this disease is considered due to military service and treated at the expense of the State, and that they will receive compensation if their disability is over 10 per cent. All patients were requested to notify the hospital by letter of possible recurrences or to present themselves for follow-up examination. In view of the economic advantages it seems reasonable to believe that at least these patients, in the event of recurrences, have followed the instructions given. In cases observed for three years recurrences were noted as follows:

Recurrence of the eye manifestations was observed in a total of 50 cases, but 40 of these patients had suffered continuously from arthritis and were still being treated for it, when the eye symptoms recurred. In only 10 cases was there complete freedom from any symptoms for some time before the recurrence of the ocular symptoms. This asymptomatic interval varied from 23 days to 20 months. The interval free from eye manifestations — while arthritis persisted — varied from two days to seven months.

Urethritis recurred in six cases, in three of which no other symptoms appeared; in one case the complete triad develop-

ed with an associated epididymitis, and in one urethritis recurred three times in the course of one year. In the latter case there was a concurrent mild arthritis and, the last time the urethritis recurred, also unilateral orchitis and epididymitis. One patient developed articular swelling after the urethritis. In the cases in which only urethritis recurred there was a completely asymptomatic interval of five to 27 days, in the others one of four to 16 months. In none of these cases was recurrence of diarrhœa observed.

Recurrence of the arthritis was noted in 10 cases and in four of them it was preceded by a new diarrhœa. In five cases the arthritis recurred alone, whereas in five ocular or urogenital manifestations were superimposed. The completely asymptomatic interval varied from three to 18 months. In one case there were two recurrences after asymptomatic intervals of seven and three months. In four cases the recurrence involved only the joints (or joint) which had been affected the first time. Five patients had symptoms both in previously unaffected joints and in others, and in one case the joint originally involved remained unaffected and the symptoms were observed only in new joints.

As regards recurrences of the arthritis the series differs from Quinquand's (1874) report, according to which Reiter's disease does not tend to recur. However, recurrences of the articular, ocular and urethral manifestations have been reported several times in the recent literature, and the present series thus agrees with them (*Cf.* p. 32).

### CONCURRENT DISEASES

In addition to the involvements described above, the patients had concurrent diseases of which some had set in prior to the dysentery and some were observed simultaneously with the first symptoms of the syndrome, while others only developed later. Thus bronchitis was noted in four cases on admission and in 14 cases later. As bronchitis, however, is very common in war time and obviously, to some extent, infectious, it seems reasonable to consider that its occurrence corresponds to the conditions at

that time and is unrelated to Reiter's disease. P n e u m o n i a was noted only once, T u b . p u l m . i n v e t . in two cases, and T u b . p u l m . s a n a t a in one instance.

Nine cases of tonsillitis occurred, but all the patients were already hospitalized or on convalescent leave at the time. There were also nine cases of hypertrophic tonsils. While at the hospital one patient contracted diphtheria and another measles. Otitis media acuta occurred in five cases, in one of which there was a concurrent sinusitis and bronchitis. Gingivitis or paradentosis was noted in 14 cases, one or several carious teeth in 121 patients, and root fillings in 20. Hepatitis epidemica was diagnosed in four patients. One female patient suffered from pyelitis due to mixed infection. The serum was positive for syphilis in three cases, in one of them treatment had been started before the onset of Reiter's disease. Helminthiasis occurred in 32 cases: one patient was infected with *Ascaris lumbricoides*, all the others with *Dibothriocephalus latus*. In view of conditions in Finland no particular significance can be attached to this incidence of helminthiasis.

A private aged 21 had had a pustular eruption on the head for half a year before the onset of dysentery; as symptoms of Reiter's syndrome appeared the eruption became worse and involved the whole body. The disease was diagnosed as *impetigo herpetiformis* and the patient later developed septicæmia in connection with which suppuration began in all joints affected by Reiter's disease. The eruption healed leaving brown areas of pigmentation but the patient died, having shown symptoms of general sepsis which was probably due to the impetigo and had found favourable conditions for spreading in the organism damaged by the syndrome. *Streptococcus hæmolyticus* grew in the aspirated pus. Autopsy confirmed the diagnosis. Because of the sepsis the autopsy material was unfortunately of no value in the study of Reiter's disease. In this connection the thought suggests itself that the cases of post-dysenteric arthritis associated with joint suppuration which have been described by earlier investigators (Cf. p. 13) may well have had a similar pathogenesis.

As regards the occurrence of concurrent diseases this series of cases correspond in the main to previous ones. However, they differ from Walther's (1940 c) in showing a considerably lower

incidence of bronchitis and angina — 5.4 and 2.7 per cent respectively, as against Walther's 13.8 and 7.4 per cent. In view of the war-time conditions, however, even Walther's figures cannot be considered abnormally high. Previous studies do not contain data on the incidence of dental caries and paradentosis in Reiter's disease.

## DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

As long as no serologic or other reaction specific for Reiter's disease is known, the diagnosis must be based on the history and on other clinical data.

Whenever the typical triad develops after dysentery, diagnosis is easy. The postdysenteric cases in which there are one or two of the essential symptoms, may be looked upon as "rudimentary" forms of Reiter's disease. Diagnostic difficulties appear, however, when there has been no previous dysentery. Even then, cases with the complete triad or with two typical symptoms may be diagnosed with reasonable certainty on the basis of the clinical manifestations. But all cases showing only one of the cardinal symptoms are often difficult to differentiate from certain other diseases of the same organs. Here information regarding cases of dysentery in the immediate vicinity of the patients or a subsequent positive agglutination test for dysentery may put the examiner on the right track.

Diseases to be considered in the differential diagnosis are e.g. the Stevens-Johnson syndrome and keratosis blennorrhagica, which in some forms may strongly resemble Reiter's disease (Cf. p. 30). Differentiation may be difficult also in the case of gonorrhœal arthritis. The gono-reaction must here be regarded as a valuable aid; according to our present knowledge, it is negative in Reiter's disease. On the other hand, it should be borne in mind that the gono-reaction seems sometimes to be negative also in gonorrhœal arthritis (Klemola 1944, *etc.*). The polyarthritis in Reiter's disease differs from that due to rheumatic fever in that the symptoms of the former do not move from joint

to joint (*Cf.* p. 50) and that the latter generally responds well to salicylates and pyramidon. As regards the arthritides occurring as sequelæ of some infectious diseases — for instance scarlatina, typhoid, febris undulans, etc. — a detailed history and serological reactions are often guides to a correct diagnosis. Differential diagnosis in the case of rheumatoid arthritis may sometimes be difficult, too, for according to the literature, cases of undoubted rheumatoid arthritis may not infrequently be complicated by ocular lesions, occasionally by non-specific urethritis or a brief diarrhœa.

## PROGNOSIS

On the basis of the present series the prognosis in Reiter's disease can be considered good, this agreeing with the opinion of practically all earlier observers. The prognosis for children, old people and individuals suffering from some other concurrent disease remains undecided, as such cases were extremely rare. In no case in the series of 344 patients was Reiter's disease the direct cause of death. One patient died of general sepsis obviously due to impetigo herpetiformis which had started before the onset of Reiter's disease (Cf. p. 80). As regards the anatomy and function of the joints and various organs the recovery also seemed good, although no very far-reaching conclusions can be drawn owing to the short period of observation.

## TREATMENT

Importance was attached to improvement of the patient's general condition by means of good food and a varied diet as far as possible under war-time conditions. The patients were kept in bed as long as they had fever or carditis in the active stage. This rule was not so strictly adhered to as generally in cases of rheumatic fever, and most of the patients were fairly soon allowed to get up, at least to wash themselves and go to the lavatory, although inflammatory symptoms, such as slight fever, increased sedimentation rate, etc., continued to be present.

In the local treatment importance was attached at first to relief of pain by temporary immobilization and aspiration together with pain-relieving medication, e.g. aspirin and pyramidon. To preserve or improve the function of the affected joint, daily muscular drill similar to that in the treatment of rheumatoid arthritis was used from the early stage. This therapy seemed to be extremely valuable; for instance the small joints showed a tendency to become fixed, but, when the joint was passively flexed, a snap was heard, and mobility returned immediately. Roentgen ray treatment was tried in 16 cases at the late stage of the disease. In nine of these it seemed to be beneficial, especially for the relief of pain, but it is impossible to say on the basis of these few cases whether the effect was psychological or otherwise. Altogether 100 patients were treated with ultra short waves, but objectively the recovery was not more rapid than usual, although the treatment improved the patients' sense of well-being. In the later stages hot local or whole baths were also used after which the patients felt that their joints were more supple.

In the cases of conjunctivitis zinc-cocaine-adrenaline drops were used locally and gave symptomatic relief. On the contrary, argyrol or targesin solution and noviform ointment did not seem to produce at any rate a favourable effect. The cases of iritis and keratitis were treated with atropine-noviform ointment which seemed to give subjective and objective results, and with local heat, occasionally also with sweat baths. The cases of urethritis were not treated locally but the suppurating penile lesions were washed with chloramin solution (1:1000) to cure secondary infection, and afterwards powdered with marfanil-prontalbin. Moist eczema was treated with 1—2 per cent aluminum acetate applications. Both these treatments seemed to be of benefit. When the sex glands were affected a suspensory and lead subacetate applications were initially used, and later local heat; these measures gave at least symptomatic relief.

Medication in the great majority of cases consisted of pyramidon (ad 2.4 g. daily), salicylate (ad 8.0 g. daily), and aspirin (ad 3.0 g. daily) for several weeks, but apart from relief of pain they scarcely seemed to affect the duration of the disease. In a few cases the fever decreased while swelling and exudation persisted at their earlier level. In view of the danger of spirochætosis neosalvarsan (ad 4.35 g.) was administered in four cases. and germanin and fuadin in one, although with no notable effect. Sulphonamides (seven cases) also seemed to be of no value. Injections of calcium did not lessen the conjunctival reddening or articular swelling. Gold therapy was tried on nine patients of which three stated that they felt better. On examination no difference was noted from the other patients.

Arthigon and pyrisan (*Bacillus fæcalis alcaligenes* suspension) were used for fever therapy. The former was given to 12 patients, each receiving 7 to 12 injections. Nine of them experienced relief of some kind or other, but the objective findings resembled those obtained by gold therapy. Pyrisan was given to 120 patients: in about 4/5 of the cases each patient received 12 injections, the others receiving fewer. The interval between the injections was generally three to four days and an elevation of fever to at least 39°C. was aimed at; the fever lasted for about two to four hours.

Two-thirds of the cases treated with pyrisan showed symptomatic improvement after the rise of temperature. Five cases showed also such a striking and prompt decrease, some even disappearance of the swelling of joints and sex glands immediately after the first and second pyrisan fever, as were not observed with any of the other therapeutical mesures. Even with pyrisan, the results were not sufficiently pronounced to allow any definite conclusions to be drawn.

*It can thus be said that none of the treatments used resulted in a prompt and general improvement.*

## AETIOLOGY AND PATHOGENESIS

### AGE AND SEX

As stated on page 40 and in Table 1, the material is one-sided with regard to the patients' age and sex, as it is composed in the main of soldiers. However, it includes 34 women (=10 per cent), the oldest aged 55, and a boy of two years and eight months showing the typical triad (urethritis, conjunctivitis and polyarthritis).

The boy fell ill with dysentery simultaneously with the other members of the family. Early in August 1946 he had fever for two days and bloody diarrhoea. On August 16 he developed a bilateral conjunctivitis, a purulent urethritis was noted on August 19 and at the same time tenderness and swelling of the joints appeared (both knees and ankles and the right elbow). On September 10 blood agglutination was: typhoid neg., paratyphoid neg., Flexner (A+D+WX) pos. 1:80, and on September 20, typhoid neg., paratyphoid neg. Urine culture on September 3 was negative, and a stool culture also failed to yield any pathogenic organisms. Roentgenological examinations of the affected joints on Sept. 10 and Dec. 5 revealed no pathology. The patient showed no symptoms after less than four months.

*Reiter's disease thus seems to occur both in men and in women, and even in children.* In this respect the results differ from those earlier reports, according to which it is noted only in adult men (Cf. p. 11).

### HISTORY

In the family history comprising the patients' parents, brothers and sisters, tuberculosis was mentioned in 65 cases, rheumatic fever or rheumatoid arthritis in 35, indefinite joint pain in 14, bronchial asthma in three, urticaria in three, crusta lactea in two

## CONCURRENT DISEASES

Studies regarding focal infections and other possible causative diseases revealed nothing that might be considered of consequence. If even small dental defects are considered, the series included 121 patients with one or more carious teeth and 20 with root fillings. Although in this respect no normal material has been studied, this in all probability corresponds roughly to the average dental status in Finland also in "healthy" individuals. Gingivitis or parodontosis occurred in 14 cases, hypertrophic tonsils in nine, and nodular or diffuse non-toxic goitre in 10 cases. Bronchitis was noted only in four patients on admission. Dyspepsia was very infrequent, occurring in only four cases. Test meals showed that free hydrochloric acid was absent in 66 cases and present in 221 (Cf. p. 68). *Dibothriocephalus latus* was found in 31 cases and *Ascaris* in one.

*Physical examination on admission thus disclosed no diseases that might be of ætiological importance in Reiter's disease.*

## DYSENTERY AND REITER'S DISEASE

### INCIDENCE OF DYSENTERY AND OF REITER'S DISEASE

In his series of 334 cases 322 (96.4 per cent) had had Flexner's dysentery and only 12 patients contracted Reiter's disease without a previous diarrhoea.

Isolated cases of Flexner's dysentery occurred all through the war at the front and also among the civilian population, but the disease became very extensive on the Karelian Isthmus in the summer of 1944. No other kind of dysentery was observed in Finland during the war.

According to Kokko (1945), the epidemic started about the 20th of June, 1944, spread rapidly and to an enormous extent, and practically terminated at the end of September. It seemed to be a fairly pure Flexner epidemic, as other than Flexner's dysentery bacilli were not once observed during the entire epidemic. Of 325 examined strains 3 per cent belonged to type A, 11 per

cent to type D, 6 per cent to type H, and 80 per cent to type WX (Kokko 1945).

It is impossible to state the exact number of dysentery cases, but it has been estimated that the epidemic affected approximately 150,000 individuals. Accordingly, about 0.2 per cent of them contracted Reiter's disease. In the small local Flexner epidemics in the rest of the country occurring in 1945, at least in some of them, Reiter's disease seems to have been far more frequent. The incidence of Reiter's disease in the cases with dysentery of the present series is slightly lower than that reported in the literature (Cf. p. 10). This difference is probably due to the fact that also the mild cases of dysentery, which did not apply for medical treatment, are included in this material. Such cases, according to Kokko (1945), amounted to 25 per cent of all dysentery cases.

The cases of Reiter's disease were distributed over the different months as shown in Table 17. This distribution also corresponds to the occurrence of dysentery (Kokko 1945) — the latter at an earlier period. This is seen even more clearly in the diagram (Appendix 1, p. 113).

TABLE 17

CASES OF REITER'S DISEASE CLASSIFIED ACCORDING TO THE MONTH OF ONSET

Month of onset	No. of cases
April .....	2
May .....	1
July .....	33
August .....	209
September .....	72
October .....	13
November .....	3
December .....	1
Total .....	334

The dysentery epidemic started on June 20, 1944, and the first patients fell ill with Reiter's disease on July 15. The curve for Reiter's disease thus begins 26 days later than the dysentery curves and also reaches a maximum somewhat later. It must also be borne in mind that the patients with Reiter's disease are

entered on the curve according to the day of onset of the syndrome, whereas the dysentery cases are classified according to the date when seen by the doctor or admitted to hospital. Of the patients with dysentery 40 per cent remained in their units for more than three days before being hospitalized (Kokko 1945). Thus the peaks in the curves for Reiter's disease and for dysentery in reality differ more than indicated by the diagram. Furthermore, the dysentery epidemic could be considered practically terminated by the end of September, but several more patients contracted Reiter's disease between October 1 and 16.

Table 18 shows the onset of Reiter's disease counted from the onset of dysentery (in 10-day periods). About 2/3 of the cases thus began 11 to 30 days after the onset of the dysentery and the longest interval was over three months.

TABLE 18

ONSET OF REITER'S DISEASE COUNTED FROM THE ONSET OF DYSENTERY

Onset, days from onset of dysentery	No. of cases
1— 10 .....	57
11— 20 .....	126
21— 30 .....	74
31— 40 .....	32
41— 50 .....	14
51— 60 .....	7
61— 70 .....	3
91—100 .....	1
Total .....	314

Seven of the 20 cases not included in Table 18 had had diarrhoea, but the exact date of its onset was not known. In one case the ocular symptoms had begun six days before the diarrhoea. Six patients had had no diarrhoea, but dysentery had been very common in their units. In another six cases the clinical reports mention no diarrhoea. Bloody or bloodless diarrhoea had thus been present in 322 (96.4 per cent) out of the 334 cases of the material; after or during the diarrhoea the patients had developed Reiter's disease. On the basis of clinical, sero-bacteriological, and epidemiological findings characteristic of dysentery these cases

of diarrhoea may be regarded as cases of Flexner's dysentery (Mustakallio 1944, K     1945, etc.).

The time of onset is roughly similar to that reported in Dorendorf's (1917), Schittenhelm and Schlecht's (1918) and Walther's (1940 c and 1941) studies (Cf. p. 11).

As regards the place of onset it is notable that 10 out of the 11 cases of Reiter's disease in 1943 were isolated cases from various parts of our front, for instance the Karelian Isthmus, Syv  ri,           , etc., and only one case occurred at a training centre. The series from 1944, on the other hand — 301 cases — was distinctly grouped round definite points of the then front line, points which correspond to the highest incidence of dysentery. Behind the lines and in the rest of the country most cases occurred along the railway lines and were the more frequent the farther east the place was situated. In the map (Appendix 2, p. 114) all cases of Reiter's disease occurring in 1944 on the Karelian Isthmus are marked by red dots; they total 224 (18 cases are excluded because only the Karelian Isthmus is given as the place where the disease set in). Each red dot thus represents one case. On the same map are marked — according to K     (1945) — the cases of dysentery applying for medical treatment during the ten days (August 11 to 20, 1944) when the Flexner epidemic had reached its peak on the Karelian Isthmus. Each black dot thus represents about five cases of dysentery.

Fifteen of the 21 civilian cases from 1945 are chiefly from Flexner epidemics in Helsinki and its immediate neighbourhood; the other cases, six in number, are from more distant localities.

As regards time, locality, and incidence, the occurrence of Reiter's disease thus seems to correspond to that of Flexner's dysentery. About 0.20 per cent of the patients affected with dysentery during the extensive Flexner epidemic contracted Reiter's disease. In 96.4 per cent of the cases Reiter's disease had been preceded by Flexner's dysentery. In the majority of cases (2/3) Reiter's disease set in within 11 to 30 days from the onset of the dysentery, but the former occasionally began simultaneously with the latter, or even before it. The longest interval was over three months.

THE NATURE OF THE DYSENTERY IN THE CASES COMPLICATED  
BY REITER'S DISEASE

To obtain an answer to the question as to the correlation of Reiter's disease with the severity of the dysentery an attempt has been made to find a suitable standard for determining the degree of severity of dysentery. This naturally causes difficulties, as for instance the duration of the disease as a whole and the intensity of its symptoms are by no means always directly proportional. On the basis of these two criteria the dysentery preceding Reiter's syndrome has been divided into four degrees of severity as follows:

1) *Abortive dysentery:*

General condition good all the time, no symptoms of fever and practically no discomfort other than bloodless diarrhoea for one to two days.

2) *Mild dysentery:*

Slight disturbances in general condition and pain in the body, high fever for two or three days, diarrhoea for a maximum of seven days, or if rather mild, for 10 days, also blood in the stools and tenesms.

3) *Moderately severe dysentery:*

Disturbances in general condition considerably greater than in the preceding group; severe headache and pain in the body, great fatigue, circulatory collapse and dehydration phenomena may occur, diarrhoea lasting up to 15 days or, with mild symptoms, up to one month, bloody stools and tenesms.

4) *Severe dysentery:*

As above, but symptoms even more intense, patient severely dehydrated and fatigued, high fever for a long time and continued diarrhoea.

Mild dysentery was most common (181 cases), moderately severe dysentery being next in order (115). Abortive dysentery

was fairly infrequent (24 cases), and severe dysentery occurred only twice. A fairly similar proportion as regards severity prevailed in general in the Flexner epidemic on the Karelian Isthmus (Kokko 1945).

*Reiter's disease thus seems to occur in all these different groups of dysentery more or less in the same proportion. Accordingly, there is no relation between Reiter's disease and the severity of the dysentery.*

#### RELATION OF THE SEVERITY OF THE DYSENTERY TO THAT OF REITER'S DISEASE

The duration of Reiter's disease can be considered a standard of the degree of severity of the disease, since all the patients were treated under similar conditions. Judged by this criterion no definite correlation could be observed in this series between the severity of the dysentery and that of the subsequent Reiter's disease.

### SERO-BACTERIOLOGICAL STUDIES OF THE ÆTIOLOGY

#### a) SEROLOGICAL INVESTIGATIONS

In 309 cases Wassermann and Kahn tests and also cholesterol-Wassermann tests were made on the blood. The tests were taken once, more rarely twice, the interval between the tests varying from two months to more than a year. In 306 patients these tests were negative and in three positive. The positive reactions were due to syphilis, as shown by the detailed investigations. — Thus it seems that blood tests for syphilis are not misleadingly positive in Reiter's disease.

After a few weeks or months from the onset a gonococcal complement fixation test (gono-reaction according to Kristensen) was made on 219 patients. The test was usually carried out once, in only a small number of cases twice, and in one case three times. All reactions were negative. While Kristensen (1930) states that in gonorrhœal arthritis and epididymitis there is "practically" always a positive gono-reaction after a few weeks

or months, which also agrees with clinical experience in general, the negative reaction in this material is definitely opposed to a gonorrhœal ætiology. The gono-reaction must thus be regarded as a valuable test in the differential diagnosis of Reiter's disease, especially in differentiating cases of epididymitis due to this syndrome from gonorrhœal affections of these organs.

In 191 cases serum agglutination tests were performed for typhoid, paratyphoid, and typhus fever, and in 24 cases for *Brucella abortus* Bang. The results were as follows:

**Negative agglutination:**

Typhoid .....	196 specimens
Paratyphoid .....	196 "
Typhus .....	193 "
B. abortus Bang .....	25 "

**Positive agglutination:**

Typhoid 1: 80 .....	4 cases
" 1:160 .....	1 case
" 1:320 .....	1 "
" 1:640 .....	1 "
Paratyphoid 1: 20 .....	1 "
" 1: 40 .....	1 "
" 1: 80 .....	4 cases
" 1:160 .....	1 case
Typhoid and Paratyphoid 1:320 .....	1 "
<hr/>	
Total 15 cases	

In addition, the blood agglutination test was in one case positive for typhoid 1:80, negative for paratyphoid, positive for Weil-Felix 1:40, and positive for Flexner 1:64. These positive agglutinations for typhoid and paratyphoid seem to be attributable to vaccination, as all the cases concerned were soldiers who had been vaccinated against typhoid and paratyphoid several times, most recently in early spring 1944.

Agglutination tests for Flexner's dysentery were performed on 270 patients. Two different bacterial suspensions were used in the tests. In one of them only one old type of Flexner bacillus was used; it was from the Serological Department and called "Flexner II". The second suspension, on the other hand, was a mixture of three Flexner types isolated from this particular epidemic and contained equal amounts of type A, D and WX. A total of 196 blood agglutination tests were performed on 185 patients with the Flexner II suspension and a total of 132 tests on 85 patients with suspension Flexner A+D+WX. Twenty-three sera agglutinated the former suspension in titres of 1:4—1:160; 33 sera agglutinated the latter in titres of 1:20—1:40 and 61 in titres of 1:80—1:640.

Twenty-four agglutination tests for Flexner A+D+WX were performed from aspirated joint fluid. Positive agglutination was obtained in eight cases in titres of 1:20—1:320 (1:20=three, 1:40=two, 1:80=one, 1:256=one, and 1:320=one case), in the others negative.

Opinions have varied as to the height of the agglutination titre to be considered a proof of Flexner's dysentery. According to Kokko (1945), the figures stated in the literature have varied from 1:50 to 1:200. Mustakallio (1944), however, is of the opinion that in cases where agglutination is positive only for the Flexner bacillus, the height of the titre is not of very great importance. In such cases titres as low as 1:20—1:40 could be regarded as positive. On the basis of tests performed by Kokko (1945) with Flexner A+D+WX, agglutination in titres of 1:80 can be regarded as the limit which, together with the clinical symptoms, justifies the diagnosis of Flexner's dysentery. Unfortunately no control studies have been carried out in this series as regards serum agglutination, but the results have been compared with those obtained by Kokko (1945) from the same suspension in his control material; in 90 per cent the serum of healthy individuals and patients with diseases other than dysentery agglutinated the suspension in titres of 1:40 at the most. Exceptionally high agglutination values, however, were noted by him in pregnant women and in patients with skin lesions. In a

group of 378 healthy men Penttinen (1947) found agglutination titres of  $\leq 1:80$  in c. 10 per cent with Flexner A+D+WX suspension.

Agglutination tests for typhoid, paratyphoid, typhus, and Flexner II were made once in each of six cases of the total 12 in which dysentery was not clinically diagnosed (Cf. p. 92); the result was negative. In one case an agglutination test was made for Flexner A+D+WX, and the serum agglutinated the suspension in titres of 1:160.

Dysentery, of course, belongs serologically to a group of infectious diseases in which fairly low agglutination titres or even frankly negative results are obtained also in cases where the clinical diagnosis is supported by a positive stool culture. In view of this, the agglutination values in this series seem to favour dysentery infection. Even the cases in which no dysentery could be demonstrated by clinical means included one where the agglutination value seems to prove the diagnosis of Flexner's dysentery. It remains to be decided, however, whether the positive agglutination reactions are due to Reiter's disease or only a proof of recent or early dysentery.

*The serological tests; viz. the Wassermann and Kahn tests, gono-reaction, and agglutination tests for typhoid, paratyphoid, typhus, and B. abortus Bang were negative. On the other hand, 61 of 132 examined sera agglutinated a Flexner A+D+WX suspension in such titres (1:80—1:640) that the reaction may be regarded as confirming the diagnosis of Flexner's dysentery. Agglutination tests carried out with an old Flexner strain (Cf. p. 97) also yielded positive results in some cases.*

## b) BACTERIOLOGICAL INVESTIGATIONS

### CULTURES

The stools of 209 patients were cultured for typhoid and paratyphoid on Conradi-Drigalski agar in a total of 279 cases, with negative results. Similar urine cultures were made in 30 cases once or several times, the specimens being obtained by catheter. One culture grew *S. paratyphi B*, the others were negative.

In this one case there was either a mixed dysentery and paratyphoid infection or a laboratory error.

Stool specimens from 209 patients were cultured for dysentery on Conradi-Drigalski\* agar; the number of cultures was 290 and seven of them grew the Flexner bacillus. These seven specimens were from five different patients and yielded growth within the first to fourth week of the disease. In the case of one of these patients a stool culture was made also during the dysentery with positive result. Besides this case, stool specimens were taken only in a few cases during the dysentery. In two cases the result was positive as late as seven days before symptoms of Reiter's syndrome appeared, in the others it was either negative or for some reason or other not recorded.

The urine specimens were cultured — besides on Conradi-Drigalski agar — on a 2 per cent agar plate, and also on a 2 per cent agar plate to which had been added 5 per cent human blood. Urine cultures made in this way once or several times on 31 patients yielded no growth. Eighteen specimens of aspirated joint exudate from the knee were cultured on the same media, but failed to yield any growth.

Gonococcal cultures were made in 28 cases on McLeod medium. Swabs were obtained from the urethra in 18 cases, from the eye in nine, and from penile lesions in one case. The results were negative.

The blood was cultured in five cases in peptone water\* with negative result.

In view of the fact that the hæmolytic streptococcus might be an ætiological factor in Reiter's disease, bacteriological cultures of the pharynx were made on 110 patients. The control material consisted of 107 patients treated at the same war hospital for various internal diseases. In the first group *Streptococcus hæmolyticus* ( $\beta$ ) grew in 17 cases, whereas the result was positive

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\* According to investigations carried out later in the Sero-Bacteriological Laboratory, the number of cultures positive for dysentery is smaller on Conradi-Drigalski agar than on SS agar (Anttonen 1947).

\* Peptone water: 40 g. peptone (Parke, Davis & Co.), 2 g. glucose, 5 g. common salt, and 1000 c.c. distilled water.

in 42 patients in the control group. It is thus evident that a hæmolytic streptococcus in the pharynx is not an ætiological factor in Reiter's disease.

*Bacteriological cultures did not add to our knowledge of the ætiology of Reiter's disease.*

#### STAINING

The urinary sediment obtained by the method described on p. 53 was studied in 305 cases, and the urine obtained with catheter in 40, either once or several times (maximum 5), at intervals of about one week with the aid of Gram's method. No pathogenic bacteria were discovered (Cf. p. 53). The same sediments were stained in 169 cases for tubercle bacilli, with negative results. Urethral specimens were stained by Gram's method in 85 cases once or several times, specimens taken from the penile lesions in six, and of the ocular discharge in 10 cases. The ocular specimens revealed no bacteria, except in one case where a few gram-negative cocci were found. The penile and the urethral specimens were either free from bacteria or contained those usually found in the urethra. Forty-four specimens of aspirated synovial exudate from the knee were also stained for bacteria, with negative result.

#### DARK FIELD EXAMINATIONS AND CULTURES OF SPIROCHAETE

The finding of a spirochæte in the blood of a patient described by Reiter (1916) prompted the author to carry out dark field examinations with a view to finding possible spirochætes direct from the blood or from inflammatory discharges. For this purpose specimens were taken from 10 patients at frequent intervals, especially from the blood, but also from the urine, the urethral and ocular discharge and from the aspirated synovial fluid. The examinations were carried out at various stages of the disease and of its symptoms. The blood was generally mixed with peptone water, by which method the preparations were most distinct, but heparinized, citrated, and oxalated blood was also used. The other specimens were examined

as such or mixed with peptone water or physiological salt solution. Each specimen was studied for two to six hours at a stretch by making continually new preparations, but no micro-organisms were found.

In addition, an anærobic culture\* suited for spirochætal investigations was made from the blood of eight patients and the urine of one, according to Klein's (1943) method (modification of Fortner's method); this also gave a negative result.

#### BLOOD FILAMENTS RESEMBLING SPIROCHAETES

In the blood of all 10 patients mentioned and the urine of one, which contained also red blood cells, as well as in the blood of four healthy control persons, there were thin light threads, of the length of the diameter of one to two red cells. They were also found in several days' old peptone water cultures of the blood. They appeared to move actively with worm-like movements and resembled spirilliform organisms, but it was later found that they belonged to the "blood filaments" and hæmokonie known from the literature. These have occasionally been regarded as causative agents of various diseases, viz. as spirochaetes. Meessen (1925), and others considered them to be the causative factors of pernicious anaemia. Yet, especially Takeuchi's (1927) studies have shown that the "blood filaments" arise from red cells by means of an unusual hæmolysis and that their movements are passive and "also probably a result of molecular movement".

As regards the origin and development of "blood filaments" the findings in this material support previous assumptions (Zeller 1923, Takeuchi 1927, etc.) that their origin is in the red cells, for they were found only in such specimens which contained red cells, and it was often seen that one or several "spirilla" were adherent at one end to a red cell. It thus seems that a red cell in non-physiological surroundings ruptures and from certain red cells and under certain conditions some of the contents may escape forming threads. Such a thread may separate from the

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\* Klein's method was modified in such a way that the plates were not fastened onto a glass tray by means of plastiline, but special plates were prepared in which the top and the bottom unite like a rabbit joint. The line of junction on the outer side was carefully covered with adhesive tape. Such plates are easier to handle and remain tight.

cell and start floating about with the currents, often strongly resembling a spirilliform micro-organism.

#### SKIN TESTS WITH BACTERIAL VACCINES

It is generally known that in skin tests normal persons may react positively to even very small amounts of bacterial vaccine, and, therefore, it is very difficult to discover the bacterial allergen (Kallos 1939, etc.). As the writer had at his disposal bacteria isolated from the Flexner epidemic concerned, it was nevertheless decided to carry out skin tests on patients with Reiter's disease and on healthy control persons. For this purpose, vaccines were prepared separately from each type of Flexner bacillus — A, D, and WX — and also from *E. coli* and *Streptococcus hæmolyticus*. These vaccines were used for *intracutaneous* injections in the following dilutions:

Flexner-type A: vaccine undiluted and in dilutions of 1:10, 1:100, and 1:1000.

Flexner-type D: vaccine undiluted and in dilutions of 1:10, 1:100, 1:1000, 1:10000, and 1:100000.

Flexner-type WX: vaccine undiluted and in dilutions of 1:10 and 1:100.

*E. coli*: vaccine undiluted and in dilutions of 1:10 and 1:100.

*Streptococcus hæmolyticus*: 200 mill. bact./1 c.c. and 2000 mill. bact./1 c.c.

0.1 c.c. of all dilutions was injected intracutaneously into the patients and the controls, who were healthy individuals on the hospital staff, including only five patients (two cases of peptic ulcer, one case of rheumatoid arthritis, one of diabetes mellitus, and one of corpus alien. pulm.). With the weak dilutions the reaction was usually small and slight, forming a red patch about 10—30 mm. in diameter, but as the concentration increased the reaction became stronger, and with the undiluted vaccines it was about 60—120 mm. in diameter and also slightly tender.

Comparing the skin reactions of the patients with Reiter's disease with those of the control series no essential differences were observed. Also, the material was too small, comprising only 29

cases and 26 controls, to allow any conclusions to be drawn. No general symptoms occurred in any of the cases and the symptoms of none of the patients with Reiter's disease were aggravated.

## DISCUSSION ON THE ÆTIOLOGY AND PATHOGENESIS

As seen from above, Reiter's syndrome is not only a disease of the male; it may occur also in women and in small children. The histories of the patients and the objective findings did not disclose any other disease — with the exception of dysentery — or any other factor sufficiently marked to be considered of ætiological importance.

In the series studied a Flexner dysentery preceded Reiter's disease in 96.4 per cent of the cases. Besides, it is probable that there had been a dysentery in those cases (3.6 per cent), too, in which there was no diarrhœa, as it seems very unlikely, that persons living in the same tent or room with dysenteric patients should have escaped infection. On the other hand, the present series of cases has shown that Reiter's disease may develop after a quite mild dysentery. The assumption thus seems justifiable that the disease may appear also in cases where the patient has contracted the infection but has not had the clinical symptoms of dysentery. This opinion appears all the more justified, as we know from the investigations of Holsti (1926), *etc.*, that inflammatory processes may occur in the digestive tract even in the absence of subjective and clinically recognizable findings.

As already stated (p. 32), other diseases besides dysentery have been regarded as causative factors of Reiter's disease, *e.g.* other enteritic infections, gonorrhœal or non-specific urethritis, infections of the upper respiratory tract and of the teeth, conditions of general sepsis, furuncles. This series and experience obtained in Finland do not, however, support these assumptions, as Reiter's syndrome has not been noted in connection with these diseases although their incidence was markedly increased during the war. In particular as regards a gonorrhœal ætiology, the consistently negative results obtained in the bacteriological and serological studies do not support it.

It is natural that when the initial symptom of Reiter's syndrome is urethritis, the former is easily considered the consequence of the latter. In this series the syndrome set in with urethritis in 23.9 per cent, with joint symptoms in 23.3 per cent, with ocular symptoms in 21.9 per cent, and in the remaining cases with various combinations of these symptoms (Cf. p. 43). Hence, it appears that urethritis should not be looked upon as an ætiological disease even in the cases where it is the initial symptom, but as due to the same cause as the other symptoms of the triad.

In recent times the question of virus causation has also aroused interest (Cf. p. 35). If Reiter's syndrome, however, were a virus disease *sui generis* one would expect it to occur more often without a previous dysentery. Accordingly, it seems probable that a virus causation would only be possible in the presence of dysenteric infection.

The present material does not entirely exclude the possibility that Reiter's disease may be caused by pleuropneumonia-like organisms (Cf. p. 34). Here, however, the same applies as was stated regarding the possibility of virus causation. The spirochæte found by Reiter (1916) seems hardly to have any ætiological significance (Cf. p. 33). In addition, in his case the onset of the syndrome had been preceded by bloody diarrhœa and, consequently, dysentery as a cause cannot be ruled out.

What has been said above seems to justify the conclusion that the cases designated in the literature as post-dysenteric arthritis, Reiter's disease or syndrome, arthritis enterica, etc., are all one and the same disease and occur after dysentery infection.

The present series throws no light on the pathogenesis of Reiter's disease. It is only possible to state that a small number of patients with Flexner's dysentery (0.20 per cent) contracted Reiter's disease which, again, in the majority of cases set in at a time when different immunizing processes against the former disease are known to occur in the organism. The primary question is — why does a dysenteric infection cause Reiter's disease in so few patients? Is this due to the dysentery bacillus or to the patients themselves? The former is possible if the strains of dysentery bacilli causing Reiter's disease differ from other strains in having

a capacity for producing toxin with a tendency to injure the tissues involved in Reiter's disease. Biochemical and serological studies for the purpose of clarifying this question have not been carried out. A second hypothesis, viz. that the patients who contract Reiter's disease react differently to the dysenteric infection than do those who do not contract Reiter's disease, is also possible. If so, there may be a question of an altered reaction, for instance allergy or some other constitutional factor, a circumstance, which is supported by the familial disposition described on p. 89. Eosinophilia occurred in 33 per cent of the cases of this series. This may, of course, be a sign of an allergic reaction or state. As detailed biochemical and serological studies, however, as well as investigations of the allergic reaction have not been carried out it is impossible to draw any conclusions regarding the pathogenesis of Reiter's disease. On the other hand, it seems likely that its pathogenesis is similar to that of the arthritides occurring after different infectious diseases such as scarlatina, typhoid, febris undulans, etc. However, Reiter's disease can be distinguished even on clinical grounds from these arthritides which in most cases have a known bacterial ætiology. This may speak in favour of Reiter's syndrome being caused by the specific toxins of the dysentery bacillus.

*On the basis of this series Reiter's syndrome thus seems to occur only after dysentery, and the dysentery bacillus seems to be the causative factor also in such cases in which no dysenteric infection can be demonstrated by clinical means.*

## SUMMARY

The present series comprises 344 cases of Reiter's disease which occurred in Finland during the years 1943—1946. The majority of the cases originated in a widespread epidemic of Flexner's dysentery on the Karelian Isthmus during the war operations in the summer of 1944. Of the patients 10 per cent were women and the youngest a boy of two years.

In about 70 per cent of the cases the complete triad (articular, ocular, and urethral manifestations) was present, about 25 per cent showed two of the essential symptoms, and 5 per cent only one of them.

Articular manifestations were observed in 325 cases (97.3 per cent), of which 316 (97.2 per cent) were polyarthritic and only nine cases (2.8 per cent) monoarthritic. The joints of the lower extremities were more frequently affected than those of the upper extremities or the vertebral column — the knee joint most frequently, and the ankle next. Besides the joints, the muscles and tendons were also sometimes involved.

Eye affections occurred in 89 per cent of the cases. They set in with conjunctivitis, iritis (22 cases) and keratitis (27 cases) appearing later. The conjunctivitis was characterized by a deep cranberry red colour and a velvety surface.

The urogenital organs were involved in 79.3 per cent, urethritis being the most common manifestation (c. 90 per cent). Cystitis occurred in 22 cases, in 10 of these unaccompanied by urethritis. Nephropathy was noted in nine patients. In six of them it appeared in the form of a mild symptomatic nephrosis, two patients developed pyelonephritis and one nephritis. Penile

lesions were present in 87 cases (26 per cent), in 10 unattended by urethritis. The testes and epididymis were affected in 11 cases, in six of them there was only testicular pain and tenderness without noticeable swelling, but in three there developed a unilateral orchitis and epididymitis leading to swelling and induration; in one a bilateral epididymitis, and in one a unilateral orchitis.

Dry circumscribed pleurisy was definitely diagnosed in 26 cases (7.8 per cent), and this diagnosis seemed very probable in 48 other cases.

Carditis was noted in 23 cases: in four there were symptoms and signs of myo- and pericarditis, in 16 only myocardial, and in three only pericardial evidence.

Less common findings were stomatitis and rupia. In one man a bilateral mastitis developed and lasted for four months.

Fever was noted in 81.3 per cent of the patients; in 13.4 per cent the axillary temperature was over 39°C. (ad 40.2°C.). The duration of the fever varied from one day (12.4 per cent) to half a year. In 77 per cent it subsided, however, during the first to third week.

The sedimentation rate was normal in 8 per cent of the cases (2 to 10 mm. in one hour) and in the others increased (ad 143 mm.). A slight secondary anaemia was observed in 42 per cent of the patients. The leucocyte count varied from 10,000 to 18,000 in 15.8 per cent of the cases, being lower in the others. A "shift to the left" was found in 21 per cent of the cases, the amount of rod neutrophils being 6 to 20.5 per cent. Eosinophilia (5—11.5 per cent) was observed in 33 per cent and monocytosis (10 to 21.5 per cent) in 13.5 per cent; in 5.9 per cent the lymphocyte count ranged from 40 to 56 per cent.

About 4/5 of the cases with arthritis became asymptomatic during the treatment which lasted from two weeks to 16 months (2/3 recovered within one to five months), and in 1/5 slight joint symptoms remained after treatment from two months to three years. The duration of the conjunctivitis varied from two days to seven months (not quite 4/5 recovered already within one to four weeks), the iritis and keratitis lasted from three

weeks to five months, the urethritis one day to nine months (87 per cent recovered in one to four weeks), the cystitis one week to nine months, the orchitis one week to two months, the epididymitis three to nine months, and the penile lesions one week to seven months. The cases of carditis recovered in three to nine months.

Recurrence of the ocular lesions occurred in 50 cases, of urethritis in six, and of arthritis in 10 cases. The asymptomatic intervals varied from five days to 20 months.

On the basis of the present series it can be stated that the prognosis in Reiter's disease is good, also as regards the anatomical and functional recovery of the various organs.

None of the treatments used, *viz.* medication (salicylates, pyramidon, aspirin, salvarsan, sulphonamides, etc.), fever therapy (pyrisan), and radiation (Röntgen, short waves), seemed to bring about a rapid general recovery. On the contrary, the disease seemed to have a self-limited course.

There was a previous Flexner's dysentery in 96.4 per cent of the cases, 2/3 contracting Reiter's syndrome within 11 to 30 days from the onset of the dysentery.

Blood Wassermann and Kahn reactions and the gono-reaction were negative. Serum agglutination tests for typhoid, paratyphoid, typhus, and *B. abortus* Bang gave a negative result. On the other hand, 61 out of 132 examined sera agglutinated a Flexner A+D+WX suspension in titres of 1:80—1:640.

Bacterial cultures and dark field examinations of stools, urine, blood, and inflammatory discharge were also negative. In only five cases did the stool cultures grow the Flexner bacillus.

On the basis of this material Reiter's disease seems to occur only after dysenteric infection.

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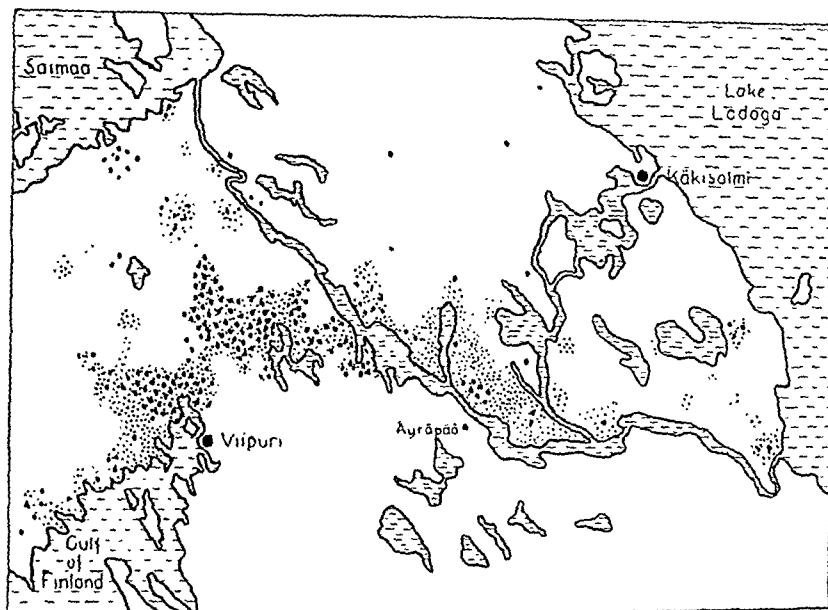
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## Appendix 2.

### MAP

(Kokko 1945)



The regional distribution of the cases of dysentery applying for medical treatment during 10 days (August 10—20, 1944) when the Flexner epidemic was at its peak on the Karelian Isthmus and of all cases of Reiter's disease occurring there during the whole epidemic. Each black point represents about five cases of dysentery, while each red point denotes one case of Reiter's disease.

The Russian attack launched on June 9, 1944 with superior force on the Karelian Isthmus stopped after 2 weeks and our front was stabilized in the main at the line: the west and north sides of Viipuri—Äyräpää—Vuoksi—Ladoga; the front remained there — except for small local variations — till the end of the war.

# ACTA MEDICA SCANDINAVICA

SUPPLEMENTUM CCXIII (213)

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STUDIA ET OPUSCULA  
IN HONOREM

EINAR MEULENGRACHT

SEXAGENARII  
AB AMICIS COLLEGISQUE CONSCRIPTA  
VII. APRILIS A. D. MCMXLVII

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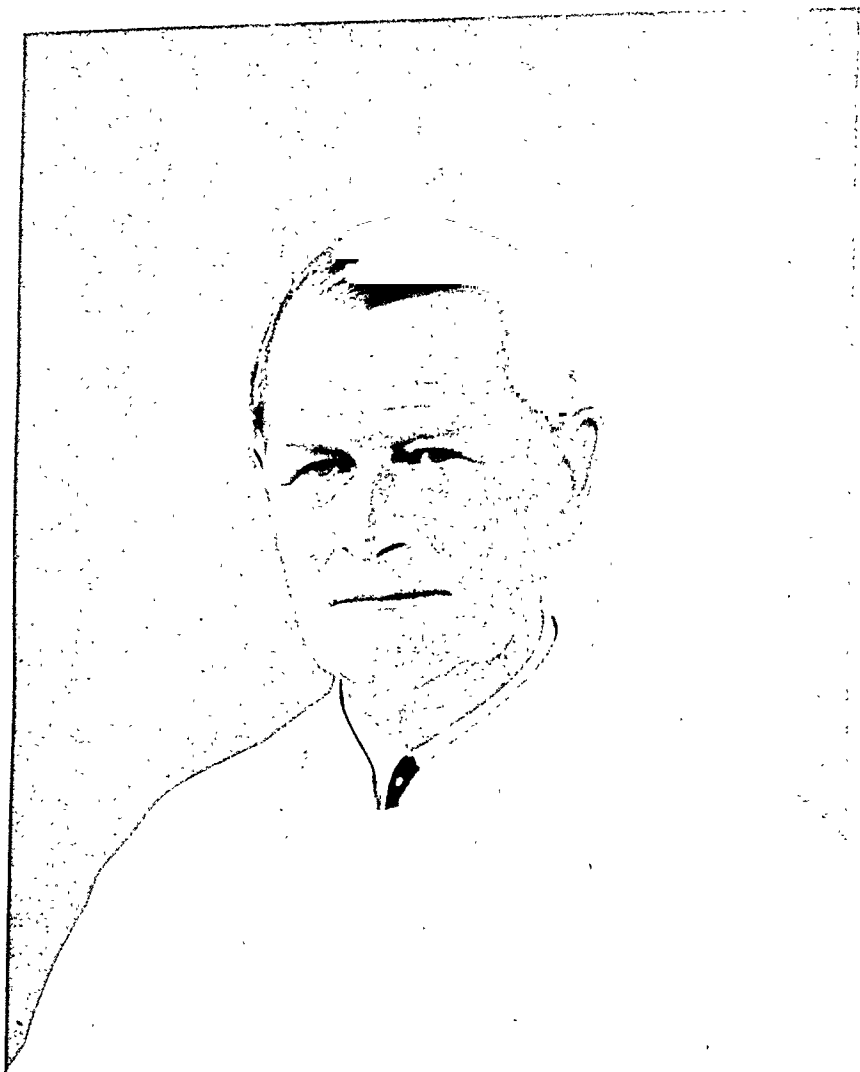
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VII. APRILIS A. D. MCMXLVII

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ROSENKILDE AND BAGGER - COPENHAGEN 1948

HOC VOLUMEN EDENDUM  
CURAVIT  
*MOGENS JERSILD*



Steuergast

ATTRIBUTED TO PROFESSOR

*EINAR MEULENGRACHT*

ON HIS SIXTIETH BIRTHDAY - THE SEVENTH OF APRIL 1947

IN RESPECTFUL ADMIRATION BY FRIENDS AND COLLEAGUES

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# CONTENTS

	Page
Preface by Erik Begtrup .....	7
Abrahamsen, H. and N. B. Krarup: On Splenectomy with special Reference to Indications .....	9
Alsted, Gunnar: The Importance of the Thymol Turbidity Reaction as a Liver Function Test .....	38
Andersen, W. Thune: Pericarditis Sicca Junenilis Benigna ..	47
Baastrup, Chr. I.: Multiple Juvenile Epiphyseal Changes .....	53
Bartels, Erik D.: Prognosis and Treatment of Massive Hae- morrhage from Gastric and Duodenal Ulcers .....	61
Bichel, Jørgen: Splenic Neutro-Thrombopenia .....	74
Bonsdorff, Bertel von: Folic Acid in the Treatment of Per- nicious Tapeworm Anemia .....	82
Borch-Madsen, P. and A. Spøborg Ohlsen: On the Effect of Total Resection of the Fundus Ventriculi in Thriving Swine upon the Anti-Anemic Factor Content of the Liver	91
Buch, Holger: Acute Hemolytic Anemia (Type Lederer) .....	99
Dameshek, William and Solomon Estren: Hypersplenism: Some Preliminary Observations .....	106
Finland, Maxwell: Studies on Influenza Made during two Epidemics in Boston .....	120
Foged, Jens: Operative Treatment of Abdominal Obesity, Especially Pendulous Abdomen .....	130
Francis, Torben: Exposure Latitude, Range of Depth (Permis- sible Variation of Depth) and Field of Applicability in Roentgenography .....	146
Gormsen, Harald: The Occurrence of Epithelioid Cell Granu- lomas in Human Bone Marrow .....	154
Grandjean, L. C.: A Case of Purpura Haemorrhagica after Administration of Quinine with Specific Thrombocyto- lysis Demonstrated in Vitro .....	165
Gripwall, Erik: The Vitamin B Complex; its Importance and Therapeutic Value in Internal Medicine .....	171
Hanssen, Olav: Chronic Lymphatic Leukaemia, Associated with Pernicious Anaemia .....	180
Hawksley, J. C.: Sloughs from Gastric Erosions .....	187
Horstmann, Paul: Possibilities of Predicting the Course of Epidemics .....	192
Iversen, Kurt: Streptococcal Pneumonia .....	200

	Page
Jacobsen, Erik and C. M. Plum: The Effect of Gastrectomy on the Blood Picture and on the Ripening Index of Reticulocytes in Rats .....	209
Jarløv, E. and N. V. Jarløv: The Postural Test .....	221
Jensen, Kai Arne and Kai Schmith: Antagonism between Sulfathiazole and Pteroylglutamic Acid ("Folic Acid") .....	234
Jersild, M.: Phagocytic Activities of Various Types of Leucocytes .....	238
Kjerulf-Jensen, K.: The Effect of Sodium Iodide Compared with that Diioda-Tyrosine on the Thyroid Gland .....	247
Ludvigsen, Svend: X-Ray Examination of Pancreas after Insufflation of Air into Stomach .....	255
Means, J. H.: Geographical Factors on Basedow's Disease ...	260
Moltke, Otto: Proctoscopy, some Technical and Clinical Notes	265
Nielsen, A. Levin: On the Mechanism of Glycosuria II. ....	273
Pedersen-Bjergaard, K., and M. Tønnesen: Sex Hormone Analyses II. ....	284
Permin, Wilhelm and Einar Thomsen: A Quinquennial Survey of 360 Cases of Abortus Provocatus .....	298
Schiødt, E.: Observations on Blood-Regeneration in Man. VI.	305
Thaysen, Eigil Hess: Osteoporosis of the Vertebral Column ..	315
Westergren, Alf: A Clinical Study of Anti-Streptolysin and Anti-Staphylolysin Titres in Acute Pleurisy .....	323
Witts, L. J.: Splenectomy in the Reticuloses .....	352

To his disciples of past years, Professor E. Meulengracht's sixtieth birthday on April 7th, 1947, appeared to be a natural occasion for doing honour to their master through the medium of a commemorative publication. A number of well-known foreign men of science expressed a wish to contribute to this publication, a most pleasing gesture, as it proves that Professor Meulengracht's importance to scientific research has spread far beyond Denmark's boundaries. As I was the first assistant to work under him while he was physician-in-chief at Bispebjerg Hospital, I shall open this publication with these few words:

If Professor Meulengracht today is one of the most well-known representatives of Danish medical research, the reasons are many. Above all, he is a worthy disciple of Knud Faber, and he has continued that sober judgment of the pathology and therapeutics of gastro-enteric diseases which was so characteristic of Faber. Moreover, he has worked with haematology as a special subject and developed it considerably. His thesis for the doctorate in 1918 on chronic hereditary haemolytic icterus is still the classical monograph on that disease. His studies on pernicious anaemia have in many ways broken new ground for his epoch-making investigations into its nosology and therapeutics, and these must be regarded as his chief contribution towards scientific research, though he has played a conspicuous part in many other branches of medical science. In all fields his success has been due to a rare ability for considering the problems with an unbiassed mind, for cutting right through prejudice and tradition and reaching his goal. Many of the facts which he established and which have made his name famous in medical science all over the world were actually very simple and plain as daylight . . . once they had been explained. The Meulengracht diet for bleeding gastric ulcer, the Meulengracht icterus index, and his colitis treatment with very limited diet, confinement to bed, and tannin clyster, are fine examples of this, and so is his description of intermittent juvenile icterus.

Inseparable from his ability to view the problems with an open mind is Professor Meulengracht's talent for organization. Thanks to this faculty his hospital department has been a model for many others, and he has seen his methods of treatment adopted far and wide. What is more, in the difficult war years his talent for organization was also of great social importance, for Denmark availed herself of it in many ways. In his work for the Danish Anti-Cancer League, on the Nutrition Committee of the National Health Service, on the Copenhagen Hospitals Committee, etc. Professor Meulengracht helped in a manner which undoubtedly facilitated and simplified the proceedings on essential points.

At the hospital he has always had a flair for making work living and interesting to those under him. All his assistants throughout the years agree that their years of work at Bispebjerg Hospital were good, free and happy years to which they look back with pleasure.

The personal charm of manner of the leader of a big hospital department is an asset that cannot be underrated, and in Professor Meulengracht's case it has contributed greatly towards frictionless relations between doctors, nurses and patients. These good relations have made the work of the department harmonious and fruitful, so that students too come there to listen to his inciting lectures and to be inspired by his positive clinical intuition.

*Erik Begtrup.*

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Medical Department B,  
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Surgeon Dept. D., (Surgeon-in-Chief: Prof. H. Abrahamsen, M. D.)*

---

## ON SPLENECTOMY WITH SPECIAL REFERENCE TO INDICATIONS

An Examination of 45 Splenectomized Patients

By

*H. Abrahamsen, M. D. and N. B. Krarup, M. D.*

The indications as to splenectomy are almost exclusively based upon clinical experience. The following conditions are generally stated as rational indications as to splenectomy: Banti's disease, hereditary hemolytic jaundice, essential thrombopenia, a few rarer affections in which the enlargement of the spleen will often afford the indication as to splenectomy (Gaucher's disease, malaria, splenic cysts, tumours) and, lastly, traumatic conditions, such as splenic rupture or torsion (23, 24, 31, 37, 40, 45).

This, however, is by no means as rational as it sounds. The diagnoses mentioned above are not always sufficiently well-defined pathological entities, but often cover more or less vague collective notions.

Examinations of splenectomized patients are therefore still of importance (28), because it is necessary constantly to try to develop the empiric basis of the operation and, through the study of the primary diagnosis, the findings at operation and the postoperative course of the disease, to try to create a greater clearness in diagnostics and safety with regard to indications (7).

The uncertainty is especially conspicuous in the case of the diagnosis Banti's disease, as there is a widespread tendency to diagnose cases of undefinable splenomegaly as Banti's disease. (7, 8). In cases of hemolytic jaundice the uncertainty is also often considerable. During recent years in particular the solitary and the so-called acquired cases have been the subject for interest

from the point of view both of etiology and treatment, and the question of splenectomy has not been finally settled as far as these forms are concerned. In the following pages we shall therefore deal with these questions in detail.

The material consists of all the patients splenectomized in the course of 20 years in the *Surgical Department D of the Bispebjerg Hospital, Copenhagen*, the distribution being as follows:

(1) "Banti's disease" .....	16 cases
(2) Hemolytic jaundice .....	12 —
(3) Thrombopenia essentialis .....	6 —
(4) Miscellaneous .....	4 —
(5) Ruptura lienis .....	7 —
Total.....	45 cases

It is in itself interesting to see how a material of splenectomized patients is distributed in this country, as there are considerable geographical variations.

*Technique.* — In removal of the spleen the procedure employed in Department D has in most cases been an oblique section parallel to the left costal margin, with complete or partial cutting of the left rectus abdominis. Through this incision the spleen is easily accessible, and a comparatively good view of its surroundings is also obtained, so that it has also been sufficiently exposed for loosening adhesions and for ligation of vessels. If, on the other hand, the stalk is short, in case the lieno-renal ligament is short, and if the cauda pancreatis is lying close to the spleen, then it will be rather difficult to apply the forceps to the vessels anteriorly; it should then be preferred to incise the ligament from behind, after the spleen has been pulled toward the ventral aspect. The vessels will then have been exposed and can be readily ligated (15, 48). The ligation was made after incision of the lieno-renal ligament in two such cases in this department and was then effected far more readily than in case the interference was made anteriorly.

In cases with a very large spleen, in which we must be prepared to meet with extensive adhesions and in which the diaphragm is not easily accessible by the abdominal route, a thoraco-abdominal incision may be involved (10). Under intra-

tracheal anaesthesia *Carter* makes an oblique incision from a point between the umbilicus and the ensiform process, extending upwards to the left to the seventh and eighth ribs as far as to the peritoneum and the pleura, both of which are opened; the diaphragm is cut through from its insertion at the costal margin to the posterior end of the incision. After application of a retractor to the ribs an excellent view of the spleen, its position and possible adhesions is obtained, thus rendering possible a ligation of the vessels under the complete control of the eyes.

In most cases the extirpation of the spleen takes place comparatively easily, but if we have to do with larger vessels, which may readily rupture when Péan's forceps or ligatures are applied, the difficulties may grow; in a couple of such cases it proved necessary to place small portions of omentum round the vessels to prevent rupture.

In three cases it was necessary to apply tamponade by means of Mikulicz's bag because of hemorrhage from the cupola of the diaphragm, and in another three cases re-operation was performed because of postoperative hemorrhage. In one case the hemorrhage came from a large vessel (slipping of the ligature? — rupture?), in two other cases from the cupola of the diaphragm; in these two latter cases tamponade had to be applied (two cases of Banti's disease, one of hemolytic jaundice). All the three patients recovered. — In addition to these postoperative hemorrhages there have no doubt been a couple of cases which must be put down to shock. A perusal of the case-records, which are of the thirties, causes one to think that a few of the patients might have been saved by a more energetic transfusion therapy. During the operations we have not observed any cases of pancreatic lesion or fistula-formation, but we have two cases of thrombosis of the vena portae, one of them moreover combined with a subphrenic abscess. It was the case of a 21-year-old woman with Banti's disease (Case No. 14) in whom a Mikulicz's bag was employed because of copious hemorrhage from the diaphragm. After removal of the bag a considerable secretion of pus occurred, and further hematemeses supervened. In spite of blood transfusion the patient died two months after the operation. The other patient, who was also operated on under the diagnosis Banti's disease (Case

No. 15), was a man, aged 55, who developed pneumonia after the operation and died a few days after the operation. Post-mortem examination moreover disclosed thrombosis of the vena portae.

Lastly, it may be mentioned that the question of accessory spleens may become of interest in cases of hemolytic jaundice or thrombopenia because such accessory spleens undoubtedly will have to be removed if the patients are to recover (12). The number of accessory spleens may vary from 1 to 10; they are most frequently situated in the vicinity of the stalk of the spleen and the cauda pancreatis, but may also be found farther off near the omentum or the mesentery, or even so far removed as at the left adnexa.

In the following each group will be gone through separately.

### I. "*Banti's Disease*".

*Introduction.* — It may be reasonable here briefly to account for the position of the problem Banti's disease. As yet it has not been fully agreed what is covered by the diagnosis Banti's disease, or even whether it actually exists as a disease *sui generis* in spite of the fact that an enormous literature on the subject has been published (36). It is a peculiar fact that nevertheless the diagnosis Banti's disease is still being employed in almost all countries, and has been able stubbornly to persist, although Banti's publications are now more than half a century old (3, 4, 5). This is partly due to the fact that by means of his way of publishing, *Banti* soon managed to bring his views to bear far and wide and, partly, that his description of the disease and his view of the syndrome still fill in a relative vacuum in pathology in so far as the ideas of certain forms of splenomegaly are extremely vague and ill-defined.

*Banti* described the disease as primary splenomegaly with progressive, indurating connective tissue proliferation (fibroadenia lienis). This was followed by anemia owing to reduced formation of blood, and finally a liver cirrhosis of the Laënnec-type developed. *Banti* imagined a toxic or infectious noxa as the cause but otherwise stressed the apparently negative etiology, as he did not include cases of known etiology, such as syphilis or malaria, in the syndrome. In histological examina-

tions he believed to be able to distinguish the changes of the spleen from those present in liver cirrhosis, but not from the changes occurring in portal sclerosis. He stressed the fact that the disease always sets on with tumour of the spleen without liver cirrhosis and thus cannot be distinguished from splenic anemia which is only a very vague concept (21).

It is generally agreed that the syndrome cannot be accepted in this form described by *Banti* as a primary affection of the splenic vessels on a toxic-infectious basis and that it hardly exists, at any rate in our latitudes (34). Nor do the histological changes in the spleen appear to be so characteristic as to afford a basis of the diagnosis and to be decisive (11). Especially with regard to the latter point there are numerous examinations and communications, but the conclusion must be the one already mentioned and, consequently, it will hardly be possible even through the most thorough histological examinations to decide whether it will be justified to maintain this concept.

During recent years, and in particular according to American views, a very great importance is now attached to the portal stasis as an etiological factor in the occurrence of splenomegaly. (30, 39, 42, 47, 48, 50). Such a portal stasis may be due to intrahepatic causes, such as liver cirrhosis. A liver cirrhosis that is not diagnosed is doubtless in most cases the actual cause of splenomegaly of apparently unknown origin (fibrosis hepato-lienalis) which is far too often termed *Banti's disease*. In particular it holds good that liver cirrhosis in children and in the young is almost always termed *Banti's disease* (34). The portal stasis may also be due to extrahepatic causes, such as fibrosis or sclerosis of the vena portae or the vena lienalis.

Other causes of splenomegaly which may be extremely difficult to differentiate are chronic infections (tuberculosis, malaria, syphilis), reticulo-endotheliosis, lymphogranulomatosis, sarcomata, non-leukemic myeloid splenomegaly (9, 35), certain cases of leukosis and *Gaucher's disease*. It will generally be less difficult to differentiate hemolytic jaundice and essential thrombopenia.

We are then left with a group of splenomegalic states which must be termed quite unknown conditions, representing a hypersplenia in which liver cirrhosis or obstructions of circulation in

the portal system, or specific disorders, cannot be demonstrated. (29). No doubt it is this group which in connection with the great differential diagnostic difficulties causes the diagnosis Banti's disease to remain so tough-lived in spite of the fact that it cannot be identified with Banti's description of the disease.

With regard to the effect of splenectomy, experience seems to show that in cases with progressive changes of the liver such as, for example, a Laënnec-cirrhosis or stenosis of the vena portae, splenectomy is generally without any beneficial effect and will often be directly contra-indicated, but in cases in which the cause of the splenomegaly is a thrombosis of the splenic veins, or cannot be determined exactly (cryptogenetic splenomegaly or hypersplenism as described above), the results of splenectomy will generally be good.

#### *Writers' Material:*

##### *Case Records.*

##### *(a) Alive and improved:*

*Case No. 1.* — Case record No. 3200/43. A driver, aged 35 years. Hematemesis and melaena 7 times in the course of 7 years. Swelling of the spleen, anemia, leukopenia with relative lymphocytosis and thrombopenia were demonstrated, normal sedimentation rate; X-raying of stomach and duodenum: Nothing abnormal. *Splenectomy* on Sept. 17th, 1943. Liver normal. Microscopical examination of the spleen: Trabeculae coarse, lymph nodes small and few, marked increase of collagenic tissue of the pulpa. *After-examination* 4 years after operation: Melaena once, a few month after operation; since then complete well-being. (Case previously reported by Bartels, 6.)

*Case No. 2.* — Case record No. 1942/42. A joiner, aged 36 years. Hematemesis and melaena repeatedly for 7 years. Considerable swelling of the spleen and anemia were demonstrated. X-raying of stomach and duodenum: Nothing abnormal. *Splenectomy* on June 1st, 1942. The liver of a somewhat greyish colour. Microscopical examination of the spleen: Marked, fibrous, sclerosing changes. *After-examination* 5 years after operation: Complete well-being since the operation.

*Case No. 3.* — Case record No. 3929/43. A woman, aged 62 years, married to a coal merchant. Fatigue, poor appetite and loss of weight throughout several years. Anemia (Hb. 42 per cent.), marked swelling of the spleen, highly increased sedimentation rate (91 mm/1 hour). Takata-Ara test ++. Sternal puncture showed in-

hibition of the marrow, splenic puncture nothing abnormal. Liver puncture: No liver tissue. *Splenectomy* on Nov. 26th, 1943. State of liver not mentioned. Microscopical examination of the spleen showed stasis and diffuse increase of the fibrillary tissue of the pulpa. *After-examination* 4 years after operation: Complete well-being since the operation.

(b) *Alive, unchanged:*

*Case No. 4.* — Case record No. 3364/45. A boy, aged 6 years, the son of a head-clerk. Always ailing, not thriving well. Swelling of the spleen, slight anemia and some degree of retardation were demonstrated. Nothing abnormal in the remaining examination. On Oct. 15th, 1945, *splenectomy* was decided on, as medical treatment proved to be quite ineffective. State of liver not mentioned. Microscopical examination of the spleen: Stasis, otherwise nothing abnormal. *After-examination* 2 years after operation: Condition completely unchanged since the operation.

(c) *Not tracked down:*

*Case No. 5.* — Case record 2377/39. A boy, aged 4 years, the son of a managing director. From his earliest boyhood he has had a severe anemia which is refractory to iron treatment. Anemia (Hb. 37 per cent., r.b.c. 1.51 mill.) and slightly increased sedimentation rate (35 mm/1 hour) were demonstrated. Sternal puncture revealed inhibition of the bone marrow. No swelling of the spleen. As medical treatment proved to be completely ineffective, and as the disorder was considered to be "anæmia splenica", it was decided to attempt *splenectomy* on Aug. 25th, 1939. State of liver not mentioned. Microscopical examination of the spleen: Nothing abnormal. *After-examination:* The patient could not be tracked down (is resident in Iceland).

(d) *Dead at time of after-examination:*

*Case No. 6.* — Case record No. 2966/32. A boy, aged 4 years, the son of a civil engineer. Copious hematemesis twice in the course of 6 months. A very considerable swelling of the spleen was demonstrated. *Splenectomy* on Nov. 25th, 1932. Liver of normal appearance. Microscopical examination of the spleen: Considerable hyperplasia of the reticular tissue, which has undergone fibrous transformation. *After-examination:* Renewed hematemesis a few months after the operation. Died on Jan. 1st, 1935. Post-mortem examination revealed liver cirrhosis and nephrolithiasis.

*Case No. 7.* — Case record No. 1785/28. A boy, aged 10 years, the son of a weaver. Had for several years been suffering from ascites which was first considered to be tuberculous but, gradually, swelling of the liver and the spleen was disclosed. *Splenectomy* on Aug. 29th, 1928. Liver atrophic, shagreened, of firm consistency, with

fibrous coatings. Microscopical examination of the spleen: Marked connective tissue proliferation with hyalin degeneration. The vessels highly sclerosed. Few follicles. *After-examination*: Died on Jan. 16th, 1929. Post-mortem examination: Status post splenectomiam, cirrhosis hepatis, perihepatitis hyalinofibrosa, ascites, pleuritis exsudativa sin., thrombosis v. cavae et hepaticae inf., nefrolithiasis sin.

*Case No. 8.* — Case record No. 101/30. A driver, aged 63 years. Had for 6 months been suffering from fatigue, abdominal oppression, poor appetite, loss of weight, melaena on several occasions. Swelling of the liver and very considerable swelling of the spleen, anemia (Hb. 61 per cent., r.b.c. 3.15 mill., w.b.c. 2150, differential count normal). Sedimentation rate 24 mm, normal icterus index (Meulengracht); X-raying of stomach and intestines: Nothing abnormal; steth. pulm. mitral incompetence, temperature subfebrile. *Splenectomy* on Dec. 9th, 1929. State of liver not mentioned. Microscopical examination of the spleen: Hyperplasia of the reticulo-endothelial tissue; the trabeculae and the lymph nodes normal. The picture mostly resembles that of a chronic infection with hyperplasia of the spleen. *After-examination*: Died on April 10th, 1930. Post-mortem examination: Endocarditis acuta in chronica valvulae mitralis, splenectomy antea. (Case previously reported by Bartels, 6.)

*Case No. 9.* — Case record No. 2462/36. A man, aged 20 years, employed as a corresponding clerk. Repeated hematemesis and melaena, pain in right side of the abdomen for 1 year. Swelling of the spleen, leukopenia and thrombopenia were demonstrated. Normal sedimentation rate. X-raying of stomach and duodenum: Nothing abnormal. *Splenectomy* on Sept. 15th, 1936. The liver displayed nothing abnormal. Microscopical examination of the spleen: No fibro-adenia but some hyperplasia of the reticulo-endothelial tissue. *After-examination*: Repeated hematemeses during the years following the operation. Died on April 4th, 1939: suicide. No post-mortem examination.

*Case No. 10.* — Case record No. 2913/38. A shoemaker, aged 43 years. Repeated hematemeses for some months. A very considerable swelling of the spleen was demonstrated. X-raying of stomach and duodenum: Nothing abnormal. *Splenectomy* on Feb. 16th, 1938. The liver was small, cirrhotic and firm. Microscopical examination of the spleen: Trabeculae and capsule sclerosed, with considerable periarterial fibrosis. Few follicles. *After-examination*: In the course of the year after the operation a considerable ascites developed. Died on March 19th, 1939. Diagnosis on certificate of death: Mb. Banti, coma hepaticum. — No post-mortem examination.

*Case No. 11.* — Case record No. 2601/37. A boy, aged 4 years, the son of an unmarried woman. Repeated hematemeses for 1 year. A considerable swelling of the spleen and slight anemia were demonstrated. *Splenectomy* on Oct. 16th 1937. Liver of normal appearance, consistency and colour. Microscopical examination of the spleen: The pulpa is the seat of considerable changes with marked sclerosis and hyalinized thickening of the connective tissue around the arteries. The sinus has collapsed. Number of cells normal. *After-examination:* Died on Sept. 26th, 1938. *Diagnosis* on certificate of death: Hæmatemesis m. g., Mb. Banti, splenectomiae seq. No post-mortem examination.

*Case No. 12.* — Case record No. 2075/38. A boot and shoe worker, aged 59. For about 4 months he had had abdominal pain, loss of weight, sluggish bowels. It was believed that a considerable swelling of the spleen could be palpated and that it must be a case of reticulo-endotheliosis or of Banti's disease. *Splenectomy* on July 5th, 1938. No abdominal tumour is found at the operation. Microscopical examination of the spleen: Apart from stasis, nothing abnormal. *Course:* Ascites developed, the patient was sinking and died on Nov. 6th, 1938. *Post-mortem examination* revealed a cancer caudae pancreatis, metastasis ad hepar.

(e) *Died soon after operation:*

*Case No. 13.* — Case record No. 838/37. A woman, aged 63 years, married to a tram-driver. Increasing oedemata and ascites for 6 months. Distinct venous markings on the abdomen. The spleen extended 10 cm. below the costal margin; anemia and leukopenia. *Splenectomy* on April 7th, 1937. State of liver not mentioned. Microscopical examination of the spleen: The pulpa highly congested. On the whole, a greatly increased number of cells, in particular of reticulum cells. No sclerosing. No increase of connective tissue. Microscopical diagnosis: Hyperplasia subchronica lienis c. stasis. — *Course:* Was sinking after the operation and died on April 10th, 1937. *Post-mortem examination:* Hepatitis chron. m. g. (Microscopical examination: The parenchyma degenerated, the structure blurred by strands of connective tissue of irregular width, with round-cell infiltration and hemorrhages, separating the lobuli), splenectomiae seq., degeneratio myocardii.

*Case No. 14.* — Case record No. 662/42. An unmarried woman, aged 21 years. Had been fatigued, poorly and anemic for many years. Very marked swelling of the spleen and severe anemia, leukopenia and thrombopenia were demonstrated. The anemia was considered indicative of splenomegalic inhibition of the marrow. Sternal puncture showed considerable hyperplasia of the

marrow, otherwise nothing abnormal. *Splenectomy* on Jan. 3rd, 1942. State of liver not mentioned. Microscopical examination of the spleen showed a thickened capsule, few follicles, some proliferation of the fibrous parts. *Course*: The patient was sinking, developed hematemesis and died on March 4th, 1942. *Post-mortem examination*: Abscessus subphrenicus sin., thrombosis v. portae, varices oesophagi, splenectomiae seq. (No signs of liver cirrhosis).

*Case No. 15.* — Case record No. 2319/31. A driver, aged 55 years. Anemia for about 1 year (Hb. 57 per cent., r.b.c. 3.48 mill., w.b.c. 16,500, differential count normal, blood platelets 500,000). Further, considerable swelling of the spleen and ascites. *Splenectomy* on Oct. 20th, 1931. State of liver not mentioned. Microscopical examination of the spleen: Leukæmia myeloides. *Course*: Was sinking gradually and died on Oct. 29th, 1931. *Post-mortem examination*: Leukæmia myeloides.

*Case No. 16.* — Case record No. 322/28. A dairyman, aged 52 years. Fatigue and increasing ascites for about 1 year. Wassermann's test was positive and there was a slightly increased icterus index and anemia (icterus index (Meulengracht) 15, Hb. 68 per cent., r.b.c. 3.32 mill., w.b.c. 2000, blood platelets 74,000). *Splenectomy* on Feb. 14th, 1928. Liver small, firm, lobate, with numerous adhesions. Microscopical examination of the spleen: The organ displayed dissemination with numerous nodes, varying in size from that of peas to that of plums, and proving to be gummata. *Course*: The patient was sinking rapidly and died on Feb. 18th, 1928. *Post-mortem examination*: Hepar lobatum, arterio-sclerosis.

*Epicrisis*: Out of regard to space, the case records are reported as briefly as possible, and the rule is that only positive findings of direct importance are included. 16 patients in all (8 men, 3 women and 5 children) have been splenectomized on the supposition that they were cases of Banti's disease. One patient could not be identified (Case No. 5). When after-examination took place, only 4 out of the remaining 15 patients were alive. 3 out of these 4 patients had materially improved (Case Nos. 1, 2 and 3), the condition being unchanged in one patient (Case No. 4). 7 out of the remaining 11 patients died from 3 months to 2½ years after the operation, and 4 died immediately after the operation. Considered as a whole, the results of the splenectomies in this group of patients have not been exactly encouraging and they call directly for a closer analysis

and critical review of the diagnoses on the basis of the considerations stated above.

*Discussion:* — The three cases that improved materially after splenectomy seem to have been of the group in which the cause of the splenomegaly cannot with certainty be ascertained and may be either thrombosis of the splenic veins or cryptogenetic splenomegaly (hypersplenism). It is worth noting that, clinically, Case No. 3 displayed symptoms of liver cirrhosis (increased sedimentation rate, positive Takata-Ara reaction, no liver tissue on biopsy) but still improved considerably after the operation. It may be seen that, even in the presence of liver cirrhosis, a considerable improvement may occur, at any rate for some time, and this fact contributes towards rendering the question of indications so extremely difficult.

In Case No. 4 the retardation, which was considered to be splenogenic, was the main indication as to splenectomy but this was without any beneficial effect, and the retardation must have been of another causation.

Case No. 5 cannot be more closely estimated.

Nos. 6 and 7 were cases of liver cirrhosis in children, which, as previously mentioned, are very often misjudged as Banti's disease. In both cases the result of splenectomy was bad.

Nos. 9, 10, 11 and 13 were in all probability also cases of liver cirrhosis. The fact that the appearance of the liver in Nos. 9 and 11 was described as normal at the laparotomy does not preclude this view.

In Case No. 14 splenomegaly may possibly have been caused by thrombosis of the v. portae, but the case cannot be more closely estimated as the patient died of a complication to the operation.

Lastly, Nos. 8, 12, 15 and 16 are cases constituting a group of their own, the splenomegaly having been of quite a different causation in these cases, respectively endocarditis lenta, cancer, leukosis and syphilis.

Summarizing, a revision of the diagnoses on the basis of post-mortem findings and after-examination shows the following distribution of the 16 patients who were splenectomized because they displayed a clinical picture resembling Banti's disease: —

Six were cases of liver cirrhosis of such a nature that the splenectomy was ineffective (including two children) (Nos. 6, 7, 9, 10, 11 and 13).

Three, possibly four, were cases of thrombosis of the splenic veins, possibly cryptogenic splenomegaly with little or no liver cirrhosis. Three of the patients in this group have improved materially after splenectomy, one died of a complication to the operation (Nos. 1, 2, 3 and 14).

Five were cases of quite a different nature (retardation of unknown causation, endocarditis lenta, cancer, leukosis, syphilis, respectively Nos. 4, 8, 12, 15 and 16); splenectomy was ineffective or directly harmful in these cases.

One case could not be tracked down.

The conclusion of these deliberations and examinations must be that it would be most expedient not to use the diagnosis Banti's disease in clinical work at all. This diagnosis is a collective concept which, under practical conditions, proves to conceal important differential diagnostic problems and thus contributes towards obscuring the indications as to splenectomy.

In cases of splenomegaly, with or without anemia, the primary task, which requires much of the medical man, must be an attempt at revealing whether there is any specific disorder underlying the splenomegaly (leukosis, non-leukemic myeloid splenomegaly, lymphogranulomatosis, reticulo-endotheliosis, Gaucher's disease, tumour, tuberculosis, syphilis). If so, the diagnosis must be established accordingly, possibly with the addition "cum splenomegalia". Splenectomy will almost always be contra-indicated.

The next step must be to try by all available means (functional tests, examination of the serum proteins, liver biopsy, possibly explorative laparotomy) to find out whether there is a liver cirrhosis and, if so, to ascertain its nature and degree. In such cases the diagnosis must be cirrhosis adding the supposed cause of the cirrhosis (hepatitidis seq., hepatitis alcoholica, thrombosis s. sclerosis v. portae). Splenectomy will almost always be contra-indicated, even if it cannot quite be denied that in certain cases with none too marked hepatic changes it may improve the condition for some time.

The diagnosis thrombosis venae portae sive venae lienalis

will often be extremely difficult and without laparotomy it can, as a rule, only be a supposition. If the thrombosis is chiefly located in the splenic vein, and if there are no hepatic changes of importance, then splenectomy is well-indicated.

This leaves a group in which it will be impossible, even by means of laparotomy, to define the cause of the splenomegaly. In such cases the diagnosis should be cryptogenetic splenomegaly or hypersplenism, possibly with the addition "sine affectione hepatis" (Bartels, 6). Splenectomy will be indicated as an attempt and will often bring about a striking improvement.

## II. Hemolytic Jaundice.

*Introduction.* — During recent years hemolytic jaundice has again been the subject for great interest. As early as in the classical descriptions by *Chauffard*, *Widal* and *Troisier* (cit. 13), it was mentioned that both congenital and acquired cases of the disease occur. In his well-known monograph (1918) *Meulengracht* (32), thoroughly examined 24 hereditary familial cases and 7 isolated cases. *Meulengracht* mentions the possibility that isolated cases may be "progenitors" and that acquired cases do not constitute a nosological entity but are due to various morbid conditions, such as pernicious anemia, the anemia of pregnancy, Banti's disease, or are merely cryptogenetic. These last-mentioned cases completely resemble the hereditary cases but are essentially different from them, as they are caused by exogenous factors and are not hereditary. *Dameshek & Schwartz* (1940) (13), divide the hemolytic anemias into 1 congenital hemolytic jaundice, which may be acute, subacute or chronic, and 2 acquired hemolytic jaundice, which may be secondary after infections or intoxications, symptomatic, e.g. in leukemia and lymphogranulomatosis, or of unknown etiology with or without demonstrable hemolysins. The acquired forms may also be acute, subacute or chronic, and in certain cases fulminant, often associated with hemoglobinuria. The acute hemolytic anemia of infectious origin described by *Lederer* (1925, 1930) (25, 26), can hardly be maintained as a special nosological entity but is in reality covered completely by earlier cases of the disease that have been previously described. We do not intend here to deal with the etiology in fuller detail, but it seems as if

there is both an anomaly of the red blood corpuscles (spherocytosis, decreased resistance) and an increase of the splenic function (18). During recent years the interest has been focused in particular on the hemolysins that can be demonstrated in a number of cases (16, 43), and it is possible that thorough serological examinations may reveal hemolysins in still more cases.

Whereas it is generally accepted that splenectomy is the only effective treatment in chronic hereditary cases, this operation has been warned against by the surgeons in acute cases (crises) and non-hereditary forms, in which treatment should consist in repeated transfusions (Greenwald, 17). This has been stressed in particular in acute cases of the so-called Lederer type. Doan (1940) (14), points out, however, that splenectomy is the proper therapy both in chronic, subacute and acute cases.

### Writers' Material:

#### Case Records.

##### (1) Hereditary cases.

###### (a) Subacute.

*Case No. 1.* — Case record No. 1314/34. A boy, aged 10 years. Typical hereditary case with symptoms for a few months. *Splenectomy* on May 1st, 1934. After-examination 13 years after operation: Complete well-being.

###### (b) Chronic.

*Case No. 2.* — Case record No. 1397/38. A man, aged 42 years. Typical hereditary case with symptoms for about 20 years, including 4 severe crises. *Splenectomy* on May 16th, 1938. After-examination 9 years after operation: Complete well-being.

*Case No. 3.* — Case record No. 811/30. A boy, aged 10 years. Typical hereditary case with symptoms from the age of 1 or 2 years. *Splenectomy* on April 3rd, 1930. After-examination 17 years after operation: Complete well-being.

*Case No. 4.* — Case record No. 164/28. A woman, aged 30 years. Typical hereditary case with symptoms since girlhood. *Splenectomy* on Nov. 28th, 1927. After-examination 20 years after operation: Complete well-being.

*Case No. 5.* — Case record No. 1080/33. A woman, aged 50 years. Typical hereditary case with symptoms for many years. *Splenec-*

tomy on March 22nd, 1933. After-examination 1 year after operation: Complete well-being. Patient could not be tracked down since then.

Case No. 6. — Case record No. 1555/44. A woman, aged 50 years. Typical hereditary case with symptoms for 10 years. *Splenectomy* on May 8th, 1944. Developed pneumonia and pericarditis after operation. Died on May 12th, 1944.

## (2) Isolated cases.

### (a) Acute.

Case No. 7. — Case record No. 834/47. A man, aged 19 years. No similar cases in his family. The onset of the disease was quite acute with symptoms resembling influenza, high fever, dedolations, articular affections, followed by fatigue and anemia.

Examination of the blood: Icterus index (Meulengracht) 8--16. Hb. 44 per cent., r.b.c. 1.35 mill., w.b.c. 3900, differential count normal. Moderate anisocytosis, no spherocytosis, mean diameter of r.b.c.  $7.6\ \mu$ , reticulocytes 10 to 14 per cent., osmotic resistance: Incipient hemolysis 0.52 — complete 0.34.

During his stay in hospital repeated severe crises, with symptoms such as described, in each case with excellent but quite transient effect of transfusion. After 5 transfusions he was transferred for *splenectomy* on Feb. 24th, 1947. Recovered quickly after the operation; complete well-being since then. Examination of the blood shows normal conditions.

### (b) Subacute.

Case No. 8. — Case record No. 1228/46. A woman, aged 26 years. No similar cases in her family. 4 months before admission the disease set on acutely with fainting, fatigue, slight swelling of the spleen.

Examination of the blood: Icterus index (Meulengracht) 7, Hb. 46 per cent., r.b.c. 2.10 mill., w.b.c. 5500, differential count normal, + unripe r.b.c. blood platelets 254,000, reticulocytes 28 to 52 per cent., osmotic resistance: Incipient hemolysis 0.66 — complete 0.34.

*Splenectomy* on Dec. 27th, 1935. After-examination 12 years after operation: Complete well-being.

Case No. 9. — Case record No. 528/42. A girl, aged  $3\frac{1}{2}$  years. No similar cases in her family. For the last few months before admission, fatigued, anorectic, anemic, considerable swelling of the spleen.

Examination of the blood: Icterus index (Meulengracht) 14, Hb. 41 per cent., r.b.c. 2.03 mill., w.b.c. 19,300, differential count normal, blood platelets 215,000, reticulocytes 12 per cent., osmotic resistance: Incipient hemolysis 0.80 — complete 0.60.

*Splenectomy* on Oct. 9th, 1943. After-examination 3 months after operation: Is doing well. Could not be tracked down later.

(c) *Chronic.*

*Case No. 10.* — Case record No. 3322/43. A woman, aged 69 years. No similar cases in her family. Increasing anemia during the last year, gradually jaundice, slight swelling of the spleen.

Examination of the blood: Icterus index (Meulengracht) 16, Hb. 38 per cent., r.b.c. 1.4 mill., w.b.c. 9,400, differential count normal, blood platelets 396,000, osmotic resistance: Incipient hemolysis 0.62 — complete 0.38.

*Splenectomy* on Oct. 9th, 1943. Died on June 10th, 1947, of cancer renis c. metastas.

*Case No. 11.* — Case record No. 1956/28. A boy, aged 6 years. No similar cases in his family. For several years anemic, subicteric with swelling of the spleen.

Examination of the blood: Icterus index (Meulengracht) 22, Hb. 49 per cent., r.b.c. 4.0 mill., w.b.c. 12,400, blood platelets 400,000, anisopoikilocytosis, numerous nuclear erythrocytes, osmotic resistance: Incipient hemolysis 0.66, complete 0.42.

*Splenectomy* on Sept. 14th, 1928. Recovered completely after the operation. Died later after an accident.

*Case No. 12.* — Case record No. 536/28. A woman, aged 26 years. No similar cases in her family. For 17 years periods with anemia and jaundice.

Examination of the blood: Icterus index (Meulengracht) 13, Hb. 60 per cent., r.b.c. 2.60 mill., w.b.c. 3600, differential count normal, blood platelets 223,000, osmotic resistance: Incipient hemolysis 0.48 — complete 0.46.

*Splenectomy* on Jan. 24th, 1928. Pneumonia following operation. Later empyema. Died on March 17th, 1928.

*Epicrisis:* 6 out of the 12 patients with hemolytic jaundice were hereditary and the 6 others were apparently isolated cases.

One out of the 6 hereditary cases had only had symptoms for a few months. The remaining 5 were typical chronic cases. One of these patients (a woman, aged 50, chronic case) died of pneumonia and pericarditis soon after the operation. The result of operation was good in the other cases.

One out of the 6 isolated cases was quite acute, two were subacute (of a few months' duration) and three were chronic. One of these patients (a woman, aged 26 years, chronic case) died of pneumonia and empyema soon after the operation. In the other patients the result of operation was good.

The spleen was submitted to histological examination in all

the 12 cases. The examination revealed hyperplasia of reticulum cells, congestion and erythrophagocytosis.

*Discussion:* It has not been possible on the existing basis more exactly to classify the isolated cases reported above. Any connection between the hemolytic anemia in Case 10 and the renal cancer which caused the patient's death 3 years later is hardly possible.

The cases include only one really acute case (No. 7). This one corresponds closely to those described as cases of Lederer anemia. Whenever employed during the crises, transfusion was also of quite an amazing effect but it was only transient, and splenectomy was required on vital indication. The result was excellent and the operation saved the patient's life. Since then he has been in good health and fit for work.

Apart from the operation mortality, the results of the splenectomies were on the whole excellent, irrespective of the nature of the cases.

*Conclusion:* The results seem to confirm the view that splenectomy is the therapy of choice in subacute and chronic cases, but the therapy of necessity in acute, critical cases (Doan, 14).

It appears, however, from the literature that one or more transfusions will often be able to cure the patient in acquired cases of the disease (19, 41, 51). In isolated cases, transfusion should, therefore, always be energetically attempted before splenectomy is decided on.

By means of serological examinations with a view to hemolysins we may probably in future be enabled to differentiate the individual cases more precisely, thus arriving at still more correct lines of treatment.

### III. *Essential Thrombopenia.*

*Introduction.* — Since Kaznelson (22), in 1916 reported the first case of splenectomy in essential thrombopenia, large collective statistics (among others by Whipple, 1926 (49), Spence, 1928 (44), Quenu, 1929 (38), have been published, showing good results of the splenectomies in the chronic, less good in the acute cases.

This question has been dealt with by Abrahamsen and Meulengracht (2), among others (1930) who considered the risk in-

volved at operation as being not particularly great and the results to be good at once, with increase in the number of blood platelets and shortening of the time of bleeding. When viewed over a longer period, the results did have a therapeutical value but, nevertheless, were a little unsafe. The mode of action of the splenectomy is unknown but it cannot quite be disregarded that it may be the operation as such, and not the splenectomy in itself, that causes the patient's condition to change. The indications as to splenectomy are frequent severe hemorrhages in chronic cases and fatal states in acute cases. *Heinild* (1942) (20), pointed out the desirability of a rational classification of the thrombopenias as a basis of the estimation of the value of splenectomy.

#### *Writers' Material:*

##### *Case Records.*

*Case No. 1.* — Case record No. 1069/28. A woman, aged 22 years. Hemorrhagic diathesis (ecchymoses, epistaxis, menorrhagia) for several years.

Examination of the blood: Icterus index (Meulengracht)  $< 5$ , Hb. 79 per cent., r.b.c. 4.77 mill., w.b.c. 4300, differential count normal, blood platelets 5000, time of bleeding  $> 15$  minutes.

*Splenectomy* on April 30th, 1928. *After-examination* 19 years after operation: "Never before in so good health". No tendency to hemorrhage. (Case previously reported by *Abrahamsen* and *Meulengracht* (2).

*Case No. 2.* — Case record No. 1109/28. A woman, aged 24 years. Hemorrhagic diathesis for several years. Profuse hemorrhages from the nose, the gingiva, the intestines and the uterus; also, conjunctival sugillations. Examination of the blood: Icterus index (Meulengracht)  $< 5$ , Hb. 52 per cent., r.b.c. 3.10 mill., w.b.c. 5300, differential count normal.

*Splenectomy* on April 3rd, 1928. *After-examination* 19 years after operation: Has been in good health since the operation. Still some tendency to epistaxis, but decreasing with advancing age. Had been in hospital in 1946 for a mild attack of thrombopenia. (Case previously reported by *Abrahamsen* and *Meulengracht* (2).

*Case No. 3.* — Case record No. 1401/44. A woman, aged 17 years. A tendency to profuse metrorrhagia for a couple of years. No tendency to universal hemorrhage.

Examination of the blood: Icterus index (Meulengracht)  $< 5$ , Hb. 60 per cent, r.b.c. 2.51 mill., w.b.c. 5760, differential count normal, blood platelets 6000, time of bleeding 4 minutes.

*Splenectomy* on April 19th, 1944. *After-examination* 3½ years after operation: Is feeling tired and indisposed, has anemia but no tendency to bleeding.

*Case No. 4.* — Case record No. 857/32. A woman, aged 20 years. For some years a tendency to metrorrhagia and ecchymoses. Profuse hemorrhages from the nose, the gingiva, the intestines and the uterus, with conjunctival sugillations and intracranial hemorrhage.

Examination of the blood: Icterus index (Meulengracht)  $< 5$ , Hb. 45 per cent., r.b.c. 2.57 mill., w.b.c. 9500, differential count normal, blood platelets 21,000, time of bleeding  $> 15$  minutes.

*Splenectomy* on March 21st, 1932. *After-examination* 10 days after operation: Well-being, no tendency to hemorrhage, blood platelets 476,000. Died on Oct. 14th, 1944; cause of death unknown.

*Case No. 5.* — Case record No. 489/38. A girl, aged 8 years. Has been tired for 6 months, with symptoms of hemorrhagic diathesis. (Ecchymoses, hemorrhages from mucous membranes, anemia).

Examination of the blood: Hb. 18 per cent., r.b.c. 0.84 mill., w.b.c. 1530, differential count normal, blood platelets 13,000, time of bleeding 8 minutes.

*Splenectomy* on Jan. 26th, 1938. *After-examination*: Complete recovery after operation. Died of pneumococcal meningitis on Dec. 4th, 1943.

*Case No. 6.* — Case record No. 590/46. A woman, aged 63 years. Has been suffering from disorder of the heart (mitral disease) for several years. A few weeks before admission, intense purpura hemorrhagica.

Examination of the blood: Icterus index (Meulengracht)  $< 5$ , Hb. 66 per cent., w.b.c. 7400, differential count normal, blood platelets 29,000. Because of violent hemorrhagic diathesis transferred, on vital indication, for:

*Splenectomy* on Oct. 29th, 1945. Recovered soon after operation; number of blood platelets became normal. Died on Oct. 30th, 1946. Disease of the heart. Hematemesis.

*Epicrisis*: 6 cases of chronic essential thrombopenia, all of them in women. The effect of the splenectomy was immediately good in all the cases. 3 patients died later on, one of unknown cause (12 years after the operation), one of pneumococcal

meningitis (6 years after the operation) and of disease of the heart and hematemesis (1 year after the operation).

*Discussion:* In all the 6 cases the condition changed immediately after the operation and none of the patients died then. One out of the 6 patients died later of hematemesis; in the remaining number of cases the operation seems to have been successful also for a longer period. A rational etiological classification of the cases is not possible on the basis of the existing information. All the cases must be considered to be of the more chronic form, but a couple of the patients had so severe acute hemorrhages in the otherwise chronic course that splenectomy was performed on vital indication. There are two young women (Case Nos. 2 and 4) of this category, who were admitted with profuse hemorrhages from the nose, the gingiva, the intestines and the uterus, with conjunctival sugillations and, in one of these patients, also with signs of intracranial hemorrhage, as she had rigidity of the neck, was somnolent and her spinal fluid contained red blood corpuscles; in both patients the hemoglobin percentage was about 50 and the number of blood platelets about 20,000. At that time (1928, 1932) it was considered hopeless to operate on such cases (Congrès Français de Chirurgie 1932, 1). By means of repeated blood transfusions before, during and after splenectomy (each patient having 3 litres of blood) both patients were, however, saved.

*Conclusion:* The results confirm what has been stated above that splenectomy is indicated in chronic cases of essential thrombopenia with severe hemorrhages but can only be performed under the shelter of transfusions.

#### IV. Miscellaneous Cases.

As mentioned in the introduction, there are a few rarer cases in which, as a rule, the enlargement proper of the spleen affords the indication as to splenectomy.

#### Writers' Material:

##### *Case Records.*

*Case No. 1. — Diagnosis: Gaucher's disease.* Case record No. 2773/34. A man, aged 48 years. Chronic bronchitis for several years. Admitted because of constantly increasing abdominal tumour. It

proved to be a swelling of the spleen of disabling size. *Splenectomy* on Sept. 29th, 1934. The spleen weighed 5 kilos. Microscopical examination of the spleen: Splenomegaly (typus Gaucher). *After-examination* 13 years after operation: Apart from bronchitis and asthma, the patient was in good health, "never gives the splenic disorder a thought". (Case previously reported by *Meulengracht* (33)).

*Case No. 2. — Diagnosis: Pick's disease.* Case records No. 833/29. A man, aged 48 years. Syphilis at the age of 21. A chronic alcoholic. Ascites of several years' standing. *Splenectomy* on June 8th, 1929. The spleen was found to be firmly surrounded by adhesions. The liver of normal appearance. Microscopical examination of the spleen: The spleen completely covered with white hyalino-fibrous coatings. Firm consistency. The capsule consists of connective tissue with collagenic hyalinized fibres. Apart from slight chronic stasis, the splenic tissue proper displays nothing unquestionably abnormal. Microscopical diagnosis: Perisplenitis hyalino-fibrosa. *After-examination*: Persistent ascites after operation. Died on Aug. 27th, 1930. Diagnosis on certificate of death: Mb. Pick. Varices oesophagi. No post-mortem examination.

*Case No. 3. — Diagnosis: Splenomegaly, malaria.* Case record No. 2766/37. A woman, aged 48 years. Malaria while in Italy 8 years before admission. During the last few years pain in the spleen and considerable swelling of the organ, gradually disabling her so that she was transferred for *Splenectomy* on Oct. 15th, 1937. The liver of natural appearance. Microscopical examination of the spleen: Increase of connective tissue, but otherwise nothing unquestionably abnormal. *After-examination* 10 years after operation: Still fatigued and poorly. In 1939 pernicious anemia was ascertained.

*Case No. 4. — Diagnosis: Cystis lienis.* Case record No. 4004/46. A man, aged 36 years. Admitted for operation for duodenal ulcer because of abdominal pain. X-raying revealed no duodenal ulcer, but a spherical calcified cyst in the spleen. *Splenectomy* on Nov. 25th, 1946. The spleen had been transformed into a unilocular cyst, hard as stone and the size of a child's head, its wall being a 2 mm. thick hard chalk plate. On one side of this cyst there remains some splenic tissue of macroscopically normal appearance. The cyst was found to contain a milky thin fluid.

*Epicrisis*: 4 patients were operated on because of splenomegaly, the enlargement of the spleen affording the indication as to operation. The respective diagnoses were: Gaucher's disease, Pick's disease, malaria and splenic cyst.

*Discussion*: Case No. 1 (Gaucher's disease) has been previously

reported by *Menlengracht* (33), who concluded that we ought to advise splenectomy as soon as the swelling of the spleen begins to cause inconvenience, and not to wait too long, as the risk involved in the operation will then become considerably greater.

Pick's disease (chronic peritonitis with perihepatitis and perisplenitis) is generally no indication as to splenectomy, and the attempt at alleviating the patient's condition seems to have been unsuccessful also in the present case. Pathogenetically it will generally be a *concretio pericardii cum corde* giving rise to a so-called pericarditic pseudocirrhosis of the liver. In most cases the etiology is quite uncertain. In suitable cases the most rational treatment will be cardiolysis.

Cases of chronic malaria or sequelae of this disease are of extremely rare occurrence in Denmark. The indication as to splenectomy is exclusively mechanical inconvenience caused by the splenomegaly.

Splenic cysts of a size giving rise to splenectomy are exceedingly rare. The case reported here is interesting in several respects: The patient was a man, aged 36 years, who had been hit by a football in the left side of the abdomen ten years ago; he had intense pain, fainted and was admitted to a provincial hospital; he was kept there for 18 days, had tenderness in the upper part of the abdomen, and was discharged in a state of well-being. Soon after discharge dyspeptic symptoms supervened, increasing as time went on. The patient also had pain in the epigastrium, without relation to the meals, however; but there was no vomiting or melaena. He now had repeated courses of treatment for gastric ulcer, at home and in hospital, but without any effect. — After his admission to Department D., X-raying revealed a spherical cystoid formation with distinct calcifications in the marginal zone, occupying the entire portion below the left diaphragm and pushing forward the stomach a little. Diagnosis: Calcified cyst. At operation a tumour, the size of a child's head and hard as stone, was found at the seat of the spleen, being closely connected with the surrounding tissue, the liver, the diaphragm and the posterior abdominal wall. Loosening and ligating the vessels was easily done and the spleen was then removed. The postoperative course was normal,

the patient being discharged free from symptoms a fortnight after the interference.

According to a statement in "General Surgery", 1946, a total of 148 cases of different types is said to have been published up to 1941. The calcified cysts are of still rarer occurrence; according to *Snoke* — also reported in "General Surgery", 1946, — such calcium cysts are said in 1945 to have been previously demonstrated only 6 times. Ours was a case of so-called "spurious cyst" or blood cyst (21), with calcification caused by a trauma. — When by means of X-raying the presence of calcium shadows is ascertained below the left costal margin — and in particular spherical shadows such as in our case — and when there has been a preceding trauma, then the diagnosis calcified cyst of the spleen is almost certain.

#### V. Rupture of the Spleen.

7 patients were splenectomized because of traumatic lesion of the spleen.

#### Case Records.

*Case No. 1.* — Case record No. 630/41. A man, aged 21 years. Immediately before admission he was jammed by a crane. Rupture of spleen ascertained. *Splenectomy* on Feb. 15th, 1941. Course uncomplicated.

*Case No. 2.* — Case record No. 731/41. A boy, aged 13 years. Shortly before admission fallen over a railing. Rupture of spleen ascertained. *Splenectomy* on Feb. 27th, 1941. Course uncomplicated.

*Case No. 3.* — Case record No. 1289/29. A boy, aged 9 years. Was run over shortly before admission. Rupture of spleen ascertained. *Splenectomy* on June 8th, 1929. Course uncomplicated.

*Case No. 4.* — Case record No. 1981/34. A woman, aged 25 years. Was run over immediately before admission. Rupture of spleen ascertained. *Splenectomy* on July 5th, 1934. Course uncomplicated.

*Case No. 5.* — Case record No. 936/41. A boy, aged 7 years. On the day before admission fallen against a kerb-stone. Signs of rupture of spleen ascertained. *Splenectomy* on March 17th, 1941. Course uncomplicated.

*Case No. 6.* — Case record No. 1716/33. A man, aged 52 years. Was run over immediately before admission. Signs of rupture of spleen. Attempt at splenectomy on July 11th, 1933. Died in course of operation. In addition to rupture of spleen, pulmonary rupture with pneumothorax and numerous other contusions.

*Case No. 7.* — Case record No. 2644/47. A woman, aged 41 years. Had a motor-car accident a fortnight before admission. On day of admission suddenly signs of intra-abdominal hemorrhage and rupture of spleen. *Splenectomy* on Aug. 4th, 1947. Well-being the first few days after operation. Died on Aug. 11th, 1947. *Post-mortem examination:* Thrombosis v. lienalis, emboliae multiplices rami intrahepat. v. portae. Infarctus anæmici multiplices hepatis, fractura costae IX + X sin.

*Discussion:* The diagnosis of rupture of the spleen may cause difficulties, not only in cases with severe hemorrhages but also in case of a small hemorrhage which may be followed by the gradual formation of a "cyst" with calcium precipitation in the peripheral part. It should also be borne in mind that some of the symptoms of severe hemorrhage, e.g. tenderness, muscular defense, may well be completely absent in case of collapse, even if there is a large quantity of blood in the peritoneum.

One out of the 7 patients with rupture of the spleen was admitted in a desolate state (Case No. 6). The wheels of a lorry had crushed two of his ribs and his spleen; when admitted, he was unconscious and deathly pale, without palpable pulse. As he improved a little after blood transfusions, splenectomy was performed but he died immediately after the operation.

Another of the case records may be mentioned in fuller detail (Case No. 7); it was the case of a woman, aged 41 years, who from July 20th to 29th was in a provincial hospital under the diagnosis fractura costarum, shock. She had a transfusion and was feeling fairly well when discharged, still somewhat tense and distended in the abdomen until, on Aug. 4th, she suddenly became dizzy and was on the point of fainting. On admission she was pale, perspiring, somewhat distant, slightly cyanotic, and there was marked tenderness below both costal margins radiating into the left flank, also slight defense in the left side of the abdomen, but no declivous dullness. She had a transfusion and, as the diagnosis rupture of the spleen was considered probable, a laparotomy was made. Large amounts of

clots were found in the peritoneum, there was a subserous hematoma the size of a hen's egg, on the surface of the spleen and the parenchyma contained several hematomata some of which had burst, opening on to the surface. Splenectomy: The course was completely satisfactory during the first 4 days; flatus was passed, and the bowels opened regularly. The abdomen remained soft, without any tenderness. The temperature daily about 38° C., pulse rate about 90. On the fifth day a sudden rise of temperature to 39° C., pulse rate 116 (shock?). In spite of transfusion and stimulants the patient died 7 days after the operation. The post-mortem examination showed the field of operation to be all right, but revealed thrombosis of the ligated vena lienalis. Liver necroses, the size of a palm, owing to embolic choking of branches of the portal vein. It is probable that the emboli have become loosened on the fourth day and given rise to the peculiar picture. The case record will be discussed in full detail in a future publication.

### Summary.

The indications as to splenectomy are still based almost exclusively on clinical experience. By way of contribution to the endeavours to create a greater clarity in diagnostics and safety with regard to indications, the patients splenectomized in the course of 20 years in the surgical department D of the Bispebjerg Hospital, Copenhagen, totalling 45, were submitted to after-examination. When the patients are grouped according to the primary diagnoses, the following classification is arrived at: —

(1) "Banti's disease" ....	16 cases	(5 children, 3 fem., 8 males)	
		4 deaths	
(2) Hemol. jaundice ....	12 —	(4 children, 6 fem., 2 males)	
		2 deaths	
(3) Essent. thrombopenia	6 —	(1 child, 5 fem., 0 males)	
		0 deaths	
(4) Miscellaneous (Gaucher's disease, cyst etc.) .....	4 —	(0 children, 1 fem., 3 males)	
		0 deaths	
(5) Splenic rupture ....	7 —	(3 children, 2 fem., 2 males)	
		2 deaths	
<hr/>		<hr/>	
45 cases		(13 children, 17 fem., 15 males)	
		8 deaths	

The introduction gives a brief reference to the surgical technique. By far the greatest number of the operations have been performed before the department took up modern anaesthetic technique and treatment of shock.

Each of the groups is then dealt with separately.

(1) "*Banti's disease*". — One of the patients could not be tracked down. Only 4 out of the remaining 15 patients were alive at the time of after-examination. 3 out of these 4 had materially improved, in one case the condition was unchanged. 7 out of the remaining 11 patients had died from 3 months to 2½ years after the operation, and 4 immediately after the operation.

A revision of the diagnoses based on post-mortem findings and after-examination showed the following distribution of the 15 patients who could be tracked down: 6 have been cases of liver cirrhosis of such a nature that the splenectomy was without any effect. 3, possibly 4, have been cases of thrombosis of the splenic vein, possibly cryptogenic splenomegaly with no or only slight liver cirrhosis. The 3 patients of this group have improved materially after the operation, one died of complication to the operation. 5 were disorders of quite a different causation (retardation of unknown cause, endocarditis lenta, cancer, leukosis, syphilis). Splenectomy was without any effect, or directly unfortunate.

It seems to be the most proper thing, not to use the diagnosis Banti's disease at all in clinical work. This diagnosis is a collective concept which, under practical conditions, proves to cloak important differential diagnostic problems, thus contributing towards obscuring the indications as to splenectomy. In cases of splenomegaly the primary task is to find out whether there is any underlying specific disorder (leukosis, non-leukemic myeloid splenomegaly, lymphogranulomatosis, reticulo-endotheliosis, Gaucher's disease, tumour, tuberculosis, syphilis). If so, splenectomy will practically always be contra-indicated. Next, we have to ascertain whether there is a liver cirrhosis and, if so, its nature and degree. If the presence of this disorder is ascertained, the diagnosis should be cirrhosis hepatitis c. splenomegalia. Splenectomy will practically always be contra-indicated, even if it cannot be entirely dismissed that in certain cases with none too marked hepatic changes it may be of a

palliative effect. The diagnosis thrombosis venae portae sive v. lienalis will be extremely difficult in many cases. If the thrombosis is chiefly located to the splenic vein and if there are no hepatic changes of importance, splenectomy will be well-indicated. There remains a group in which it is impossible more closely to define the cause of the splenomegaly. This group may be termed cryptogenetic splenomegaly or hypersplenism, possibly with the addition sine affectione hepatis. Splenectomy is indicated as an attempt and will often result in a striking improvement.

(2) *Hemolytic jaundice*. — 6 out of the 12 patients operated on were hereditary cases, the other 6 apparently being isolated cases. One out of the 6 hereditary cases was subacute, the others were chronic cases. One patient died immediately after the operation. The results of operation were good in the other cases. One out of the 6 isolated cases was acute, two were subacute and three were chronic. One patient died immediately after the operation. The results of operation were good in the other cases.

A more detailed classification of the isolated cases has not been possible on the existing basis. The results of operation confirm the view that splenectomy is the therapy of choice in subacute and chronic cases but the therapy of necessity in acute, critical cases. Transfusion should, however, always be energetically attempted before splenectomy is decided on. It is probable that by means of serological examinations with a view to the presence of hemolysins it may be possible in future more precisely to differentiate the individual cases, thus arriving at still more correct lines of treatment.

(3) *Essential thrombopenia*. — The effect of splenectomy was immediately good in all the 6 cases. One out of the 6 patients died later of hematemesis. In the other cases the operation seems to have been successful, also when viewed over a longer period. A rational etiological classification of the cases has not been possible on the basis of the existing information. All the cases must be classed among the more chronic ones. In two of the cases operation was performed on vital indication during acute aggravation. The results confirm that splenectomy is indicated in chronic cases of essential thrombopenia with frequent, severe hemorrhages.

(4) *Miscellaneous cases.* — One case of Gaucher's disease; the spleen weighed 5 kilos, the result was good. One case of Pick's disease; the result poor, the patient died one year after operation. One case of malarial spleen; the result fairly good. One case of calcified cyst in the spleen; the result good. The indication as to operation was the enlargement of the spleen in all the four cases.

(5) *Rupture of the spleen.* — 7 patients, one of whom was admitted in a desolate condition, another patient dying of thrombosis in the v. lienalis and liver necroses, the size of a palm, owing to embolic choking of branches of the v. portae 7 days after operation. The diagnosis rupture of the spleen may be difficult to establish.

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## THE IMPORTANCE OF THE THYMOL TURBIDITY REAC- TION AS A LIVER FUNCTION TEST

By  
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The thymol turbidity reaction was introduced in 1914 by MacLagan (5). He demonstrated that when serum is added to a solution of thymol in a barbital buffer solution with a pH of 7.3 a turbidity is produced. He valued the strength of the reaction by comparing the turbidity with Kingsbury's gelatin standard and found all normal serum samples to be less than 4 units. Furthermore, he showed the differential-diagnostic importance of the test in diseases of the liver, the reaction being positive, i.e.  $\geq 4$  units in 133 of 143 cases of parenchymatous liver disease. On the other hand it was positive in only 3 of 38 cases of obstructive jaundice. MacLagan suggested that the factor causing turbidity was to be found in the gamma globulins.

MacLagan's results have later been confirmed by other investigators. Watson & Rappaport (6) found a positive reaction in 45 of 77 cases of parenchymatous liver disease, but only in 2 of 12 with obstructive jaundice. They believed, furthermore, that in chronic hepatic dysfunction (cirrhosis) the thymol turbidity test is more rarely normal than the cephalin-cholesterol flocculation test. Shank & Honglund (7) found the normal values between 0 and 4.7 units while they observed elevated values in 82 of 83 cases of parenchymatous liver disease. As they considered colorimetric evaluation to be inexact they introduced spectro-photometric evaluation, using a suspension of barium sulphate as standard. Thus they obtained results agreeing perfectly with the original colorimetric units of MacLagan.

In Scandinavia Lehmann (4) has observed a positive reaction in almost 100 per cent of cases of parenchymatous liver disease,

while Brante (2), using the technique of Shank & Hoagland, has found a positive test in 15 of 23 similar cases but only in 1 of 11 cases of obstructive jaundice.

Mateer & co-workers (6) have been using the thymol test to examine the conditions in chronic subclinical liver impairment, obtaining results agreeing with those of Watson & Rappaport (8). They recommend a buffered solution with a pH of 7.55 thus making the reaction more sensitive. In 40 normals they have observed values from 0 to 1 and, consequently, they regard higher values as a sign of latent impairment of the liver.

Recently Cohen & Thompson (3) have examined by which protein fraction the reaction is caused. Evidently the thymol solution chiefly precipitates the beta globulins and the reaction is stated to be a fairly quantitative expression of the content in serum of beta globulins. On the other hand the content in serum of lipoids is stated to be without importance as to the reaction. In a big comparative investigation they have found the reaction more frequently positive in acute inflammatory processes than in chronic degenerative changes.

Since November 1946 the thymol turbidity reaction with the technique of Shank & Hoagland (7) has been used as a liver function test in Medical Department B, Frederiksberg Hospital. In the following are briefly communicated the results in a series of 115 patients, chiefly suffering from hepatic disorders. First the results of the reaction have been observed in various diseases, second its course in hepatitis and, finally, a comparative evaluation has been made between the thymol reaction and a few other liver function tests: icterus index, serum iron and Takata's reaction.

In Table 1 the collected results from all of the 115 patients are recorded, the highest values observed being shown in Mac-lagan units. The material is subdivided in jaundiced and non-jaundiced patients, the former group chiefly comprising parenchymatous liver diseases, the latter containing few of these. In 43 (83 per cent) of 52 patients suffering from acute hepatitis a positive reaction, i. e.  $> 4$  units, was observed, the reaction in 22 of these cases being above 12 units. In all of 10 patients suffering from malignant chronic or subchronic hepatitis a positive, pronouncedly elevated, reaction was seen, above 11

*Table 1.*  
The result of the thymol test in 115 patients.

	Jaundiced						Non-jaundiced					
	1	2	3	4	5	6	7	8	9	10	11	12
MacLagan units	acute hepatitis	malignant hepatitis	biliary cirrhosis	fatty degeneration	intermittent juvenile jaundice	obstructive jaundice	incipient Laennec cirrhosis	cholelithiasis cholecystitis	renal and cardiac oedema	cancer, myeloma	pneumonia	infections
above 12 . . . .	22	8										
11—12 . . . .	4	2										
10—11 . . . .	1											
9—10 . . . .	2											
8—9 . . . .	3										1	
7—8 . . . .	2			1							1	
6—7 . . . .	3					1					1	
5—6 . . . .	5							1				
4—5 . . . .	1					1					2	
3—4 . . . .	4		1					1	1	1		
2—3 . . . .	2					2			2	1	1	1
1—2 . . . .	3				1	7	1	2	1		4	2
0—1 . . . .					1	2		2	1	2	2	5
total . . . . .	52	10	1	1	2	13	1	6	5	4	12	8
thymol-positive	43	10				2					5	
per cent . . . .	83	100				15					42	

units in all of the 10 cases. It will be noticed at once that values above 9 units are met with exclusively in acute and in malignant hepatitis. Unfortunately the material does not contain a real case of atrophic cirrhosis of Laënnec, but only a single case of biliary cirrhosis running a very protracted course and another single case of latent chronic hepatitis with incipient development of cirrhosis of Laënnec, histologically distinctly different from malignant hepatitis. Both of these cases, verified by post-mortem, showed continuously a negative thymol reaction. Two young men with intermittent juvenile jaundice (Meulengracht) likewise had negative reactions.

In 13 patients suffering from obstructive jaundice a moderately positive reaction was observed in 2 (15 per cent). Finally the reaction was positive in a subicteric cachectic patient in whom the postmortem showed considerable fatty degeneration of the liver but no hepatitis or cirrhosis.

In the group comprising the non-jaundiced patients it is at

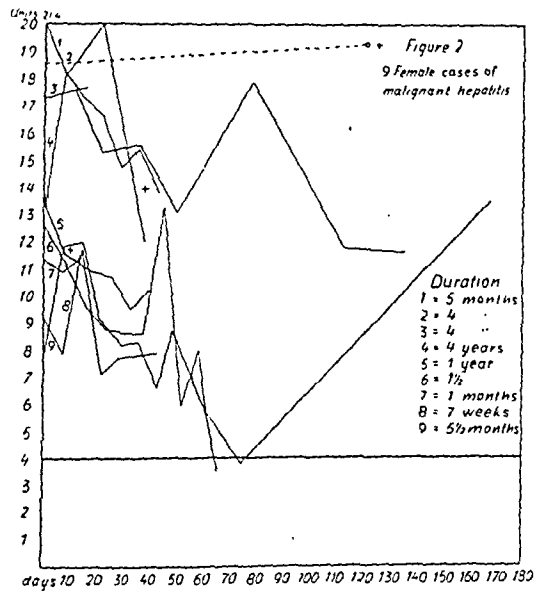
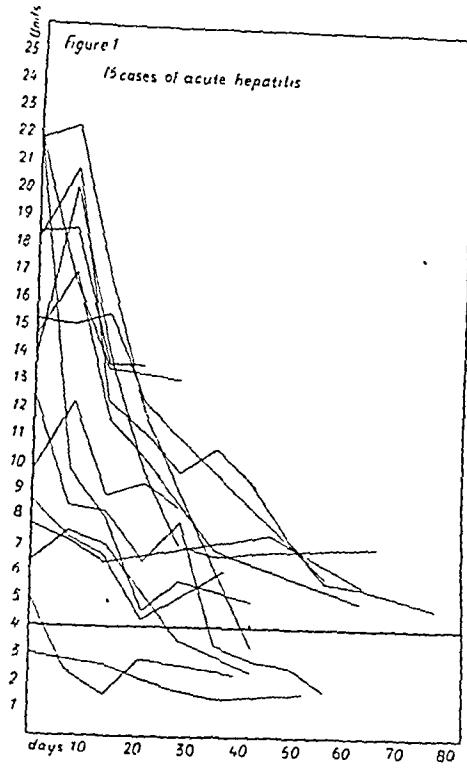
once conspicuous that the thymol turbidity test was moderately positive in about half of the pneumonia patients. This might be due to the increase of antibodies in serum, these being, presumably, attached to the gamma globulins. The latest investigations having shown that the factor causing precipitation is connected with the beta globulins it is, however, more likely that the positive reactions in pneumonia patients are due to parenchymatous liver damage, not rare in pneumonia. This conception is supported by the results in group 12, comprising patients with febrile infectious disorders and showing negative reactions in all cases examined.

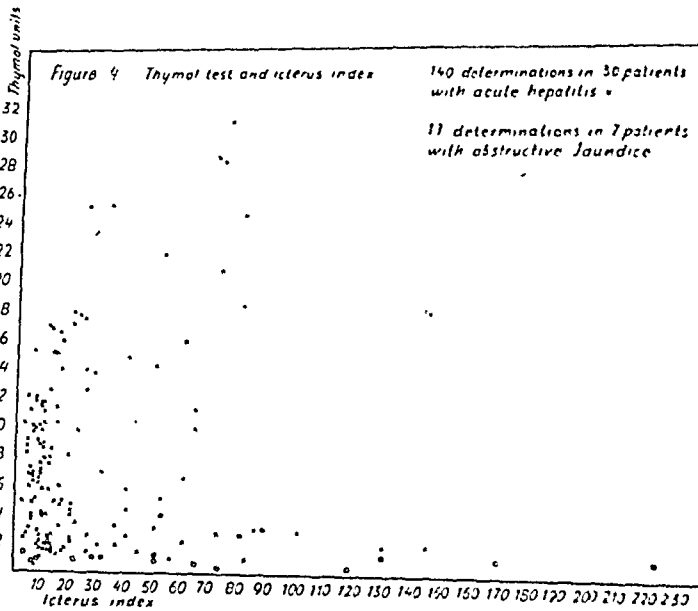
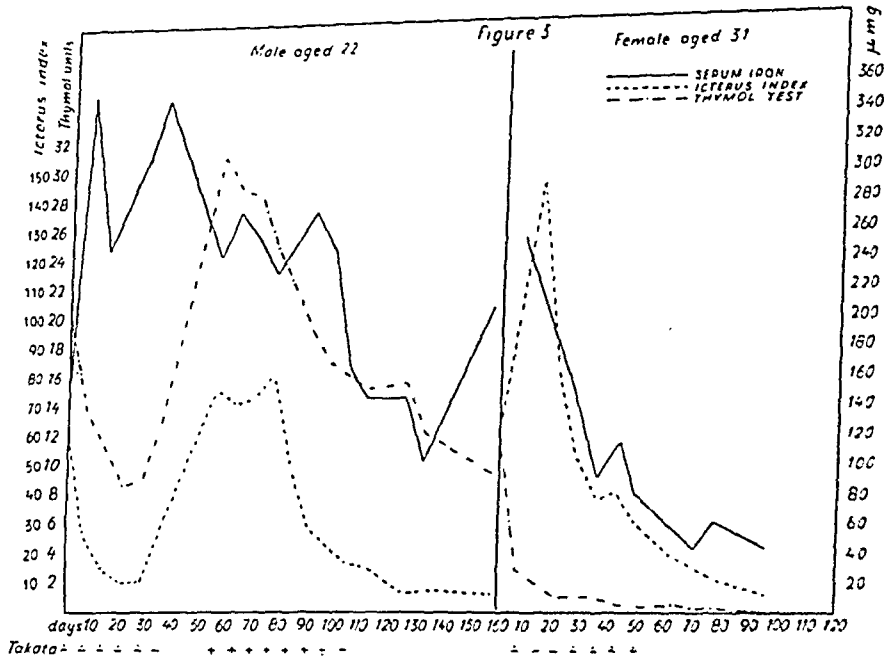
In group 9, comprising patients with cardial and renal oedema, a single positive reaction is found, probably caused by hepatic stasis. All of the few cancer cases examined turned out negative. The same applies to a case of generalized myeloma with hyperglobulinaemia to the extent of 11.6 per cent.

Thus the general result supports the conclusion that a positive thymol turbidity reaction strongly favours the diagnosis of an active parenchymatous liver disorder. Reactions above 9 units have been observed in acute and in malignant hepatitis only. In 17 per cent of all cases of acute hepatitis examined the reaction, however, has constantly turned out negative, these cases having run a course which was in no respect less severe than the remaining ones. Most likely the thymol turbidity test may be conceived as an expression of activity of the processes. In chronic parenchymatous non-infectious liver diseases the reaction is negative, as may be concluded from the 2 cases of cirrhosis reported here.

To get an idea of the course of the thymol reaction in patients with acute hepatitis a diagram has been made in figure 1, showing its course in 15 casually selected hepatitis patients. A primary increase followed by a secondary decline will be observed in about one half of the patients, while the reaction runs a declining course right from the start in the remaining patients. Normal reactions within the first two or three months will be seen in few patients only.

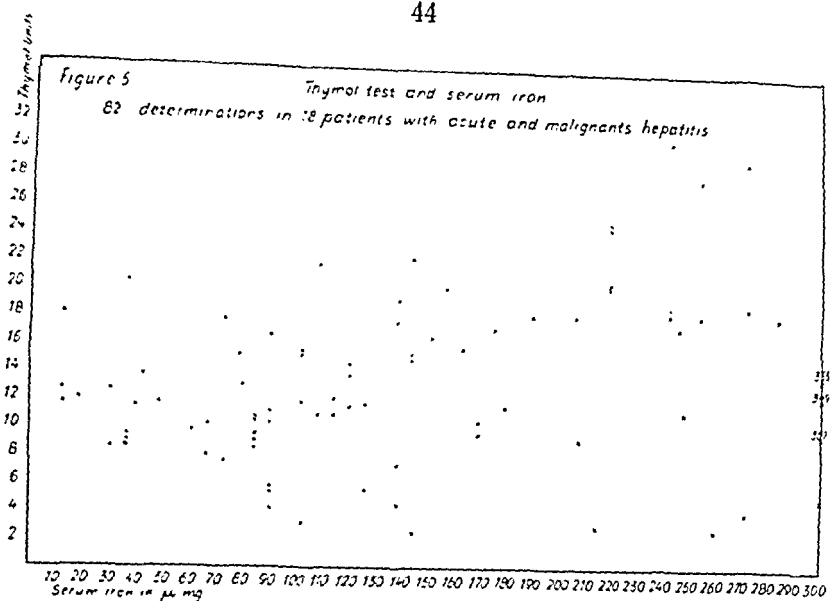
Figure 2 shows the course of the reaction in 8 women with malignant hepatitis and 1 with Banti's disease. The time interval between the beginning of the disease and the first reaction





recorded is most varying and the diagram, therefore, conveys a somewhat heterogenous and uncharacteristic impression. The curves, however, have the almost constantly increased values in common.

Figure 3 shows the thymol reaction in a young man suffering from relapsing hepatitis, and in a young woman with acute



hepatitis. The results of Takata's reaction and icterus index and serum iron have been recorded simultaneously. In the former patient the thymol reaction and icterus index run parallel courses, while the latter patient distinctly demonstrates the independent course of the two reactions. In the former patient Takata's reaction exhibits some parallelism with the thymol test, becoming positive during the relapse.

To investigate further into these problems figure 4 exhibits 140 simultaneous determinations of the thymol reaction and icterus index, carried out in 30 patients with acute hepatitis, and 17 determinations from 7 patients with obstructive jaundice. The results show that the two reactions are independent of each other.

Figure 5 demonstrates 82 simultaneous determinations of the thymol reaction and serum iron in 18 patients with acute and malignant hepatitis. Evidently these two reactions are also independent of each other and may be assumed to express two different liver functions.

Finally table 2 shows the thymol test in relation to Takata's reaction, recording 222 simultaneous thymol and Takata reactions in 63 patients, chiefly suffering from hepatitis. The evaluation is difficult as there are only 58 positive Takata reactions.

Table 2.  
Relation between the thymol test and Takata's reaction.

Thymol Reaktion	negative	Takata's Reaction			total positive
		+	++	+++	
0—4 .....	74 = 45 %	2	1	2	5 = 9 %
4—10 .....	47	13	1	2	16
10—20 .....	37	11	10	8	29
above 20 .....	6	6	1	1	8
total .....	164	32	13	13	58

All combinations between the two reactions are represented, however, a certain relation seems to exist. Among the Takata-negative samples 45 per cent have a normal thymol reaction, while among the Takata-positive ones only 9 per cent show a normal thymol reaction. The small numbers permit no further differentiation. It can hardly be concluded that the thymol test and Takata's reaction are expressions of the same liver function. The accordance observed is more likely caused by damages of the liver function, running a parallel course.

Comparing the results reported here with the extant literature shows essential accordance. The thymol turbidity test may, therefore, be regarded as a liver function test, expressing a function of the liver, previously not recorded. Applied by itself it gives, like all other liver functions tests, no certainty, particularly if negative, but in combination with other function tests it yields excellent differential-diagnostic and prognostic help. It is most valuable in the differential diagnosis between obstructive jaundice and parenchymatous disease. A strongly positive reaction indicates without any doubt a hepatitis. But also in the difficult differential diagnosis between acute benign and malignant hepatitis the thymol test is of value, especially in combination with Takata's reaction and determination of the serum iron.

Table 3.  
Result of function tests in diseases of the liver.

	Thymol test	Serum iron.	Icterus index	Takata's reaction
Acute hepatitis .....	+	+	+	÷
Malignant hepatitis .....	+	÷	+	+
Obstructive jaundice .....	÷	÷	+	÷
(Cirrhosis) .....	÷	÷	÷(+)	÷

According to the results reported here and the results in a previous paper on malignant hepatitis (1) the relation between the various liver function tests and the diseases of the liver may perhaps schematically be given as shown in table 3.

It must, however, not be forgotten that the early differentiation between benign and malignant hepatitis may be extremely difficult, and that, furthermore, no reaction is reliable to a certainty of 100 per cent. Finally the conditions as to the true cirrheses must, necessarily, be more closely investigated before any really definite statement can be made.

### *Summary.*

The thymol turbidity test has been carried out in 115 patients, chiefly suffering from diseases of the liver. The results have been observed in various pathological conditions and the course of the reaction in infectious hepatitis has been recorded. Furthermore a comparative evaluation has been made between the thymol test and various other liver function tests viz. icterus index, serum-iron and Takata's reaction. It is suggested that the thymol test expresses a liver function not previously recorded. The reaction is positive, i. e. above 4 Maclagan units, in 83 per cent of 52 cases of acute infectious hepatitis and in all of 10 cases of malignant hepatitis. It is negative in 11 of 13 cases of obstructive jaundice. In pneumonia slightly elevated values are observed in 5 of 12 cases.

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## PERICARDITIS SICCA JUVENILIS BENIGNA

By

W. Thune Andersen, M. D.

The significance of the various murmurs heard in the stethoscopy of the heart has become rather secondary since X-rays and electrocardiography have provided better means of appraising the state of the organ. It has long been realized that but little importance was to be attached to systolic murmurs. Diastolic and praesystolic murmurs are undoubtedly of more consequence, but here again it has often been the experience that they are to be heard in people with an apparently sound heart. On the other hand, a murmur that will always make the examining physician suspicious is the pericardial friction sound. When this is heard it will be usual to assume a serious infection, which makes prognosis uncertain; even if the infection is cured there will be reason for fearing the development of a Symphysis pericardii later on. And so, on going through the text-books on the subject of acute pericarditis one finds that its prognosis is set up with all possible reserve. Rheumatic infection is the cause advanced first and foremost for acute pericarditis, but it is quite likely to occur as a complication to any form of infection. Again, pericarditis of a non-infectious nature is nothing uncommon, i.e. as one of the elements in polyserositis. It may be observed in uraemia or in coronary occlusion. For the sake of completeness I may also mention that it is to be seen in the case of lesions affecting the pericardium and the intrusion of foreign bodies.

As an etiological factor in pericardial affections White states that in a large material the following causes were found:

Pneumonia 34 %, rheumatic fever 28 %, uraemia 11 %, tuberculosis 10 %, sepsis 5 %, coronary occlusion 3 %, typhoid 2 %, the remaining 7 % being unknown.

acterized as a typical pericardiac friction sound which intensifies with pressure on the stethoscope.)

Steth. pulm.: Slightly weak respiration over the entire left lung, otherwise nothing definitely abnormal.

Abdomen: Natural except for the appendectomy cicatrice.

Extremities: Natural.

Height: 188 cm.

Weight: 71 kg.

Urine: normal.

S. R.: 4 mm. — 7 mm. — 4 mm., taken three times at 14 days' intervals.

Haemoglobin: 92 %.

Blood picture: Quite normal.

W. R.: —, Mantoux: weakly +.

Electrocardiog.: Slight indication of right axis deviation, otherwise nothing definitely abnormal, especially nothing to suggest myocarditis.

X-ray: Heart quite normal.

Lungs normal, except that on the left side there was a very small pneumothorax, a border about 1 cm. wide being visible between the lung and thorax wall; it comprised only the upper third of the lung, however.

Diagnosis: Pneumothorax spontanea. Heart normal.

On later skiagrams the pneumothorax disappeared gradually, whereafter the picture became completely normal.

While in the 3rd Dept. he was given no special treatment. In the course of a month the stethoscopic changes subsided entirely. He was then allowed to get up; was a little tired the first few days, but soon got over it. On discharge he was quite symptom-free.

In 1939 it was reported that during the past five years he had been quite well and had noticed nothing at all from his heart, in spite of hard work (engineering apprentice).

## *Case Record II.*

Male, 18 years, student.

Previously quite well.

Suddenly one day in 1935 while at dinner he had a peculiar sensation in the left side of the chest, "as if something was bursting inside me", as he put it. Immediately afterwards he heard scraping, sonorous sounds synchronous with the pulse beat, so loud as to be heard by the other members of the family in the room. He did not feel ill, shocked or short of breath, but nevertheless was put to bed. His doctor summoned me, and I found the following:

Physical exam.: Quite healthy, natural appearance, tall but rather slender.

Steth. cord.: Almost corresponding to the apex there were rough, rasping, pericardiac friction sounds which were distinctly intensified on pressing the stethoscope hard. The remaining examination revealed nothing abnormal whatever.

Height: 190 cm.

Weight: 72 kg.

Urine: normal.

S. R.: 3 mm.

Electrocardiog.: Quite normal.

X-ray of heart and lungs: Quite normal.

The murmurs subsided in a few days. For safety's sake he was kept in bed for a time, but as he was then quite symptom-free and not feverish, with a normal S. R., he was allowed to get up, but warned to be careful.

Since then his heart has never troubled him, and in answer to an inquiry in 1947 I was informed that he is still quite well.

### *Case Record III.*

Male, 18 years, student.

Previously quite healthy, particularly had no heart or lung symptoms. Without any external cause he had a sudden sensation in the left side of the chest one day, as if his heart were scraping on something. He did not feel ill, or shocked, but summoned a relative who was a local practitioner. The latter found pericardial friction sounds and called me.

On examination I found a tall but rather slender young man, healthy natural appearance, not unwell or short of breath.

Steth. cord.: Rough pericardiac friction sounds over most of the precordium, otherwise nothing abnormal.

The rest was quite natural.

S. R.: 2 mm.

Urine: normal.

Electrocardiog.: normal .

Temp.: normal.

X-ray of heart and lungs: normal.

As the case was so very similar to the two previous cases, I presumed to draw an analogous conclusion from them and prognosticated a good termination, though I advised him to keep his bed until the murmurs had subsided. I have heard nothing of him since and therefore assume that the course was as in the other cases.

Not having noted his name, I am unfortunately unable to say anything of his present condition.

### *Case Record IV.*

Male, 18 years, engineering apprentice.

Admitted to the Medical Dept., Svendborg County Hospital, from

28th August to 12th September 1947. Quite well previously, inoculated against Tb. a year ago. Two days before hospitalization and quite without exterior cause, while standing still he felt a pain between the shoulder-blades, radiating from there forward to the left side of the chest. He himself had a sort of impression that he had "strained a muscle". The doctor called in found pericardiac friction sounds over the heart and therefore had him admitted here.

Physical exam.: Healthy natural, appearance, certainly not ill, no dyspnoea or cyanosis; rather tall and well built.

Steth. cord.: Borders normal. At the left sternal margin in the 4th intercostal were distinct, rough friction sounds which were intensified on pressing the stethoscope hard, whereby they had a metallic, almost gurgling character and could then also be heard by people standing round. Action slightly accelerated, regular, about 90; otherwise condition normal.

Other examinations revealed nothing at all abnormal.

Height: 173 cm.

Weight: 56 kg.

Urine: normal.

S. R.: 3 mm.

W. R.: —.

Haemoglobin: 120 %.

Blood picture: normal.

Blood pressure: 135/80.

Antistreptolysine: twice after a week, just before discharge, completely normal conditions.

While in hospital the murmurs subsided in the course of eight days, whereafter he was quite symptom-free. Electrocardiograms were taken every other day, 10 in all, and showed quite normal conditions.

The sedimentation rate on discharge was 2 mm.

X-ray of heart and lungs showed quite normal conditions both on admission and on discharge.

The temperature was normal all the time. The pulse curve during the first few days was between 80 and 100, afterwards slightly below 80.

Discharged in a state of complete health.

Here then are four cases of pericardiac friction sounds with an acute onset. The following circumstances were common to all four:

- 1) They were all male patients.
- 2) They were all about 18 years of age.
- 3) They were all over medium height, in fact two were con-

siderably over, and the attack came at a time when they were growing fast.

- 4) In all cases the attack subsided, apparently without leaving any trace.
- 5) No trace of infection was found in any of the patients. Temperature was normal, general condition especially good, sedimentation rate normal; Antistreptolysine was tested only on No. 4, but it was normal.
- 6) The murmurs were unusually loud and sonorous.

On account of these common characteristics in the four case records I consider it justifiable to draw the conclusion that the cause of the friction sounds was not pericarditis proper, but rather a rupture brought about by displacement through the marked and rapid growth. This rupture must have brought about an unevenness in the pericardium, thus giving rise to the friction murmur. It is curious that in no case is there anamnestic information of the attack starting in conjunction with physical exertion; on the contrary, in one case at any rate it came while the patient was sitting quietly at dinner. One of the patients, No. 1, had a complication, a slight spontaneous pneumothorax. In view of the above arguments, which also apply to the last-named patient, it must be said that this provides additional support for the theory of a rupture as the etiological factor. In Case 1 there was also a rupture of the pleura.

Prognosis seems to be good, at any rate for the period of observation hitherto possible. Two of the patients were quite without symptoms for five and twelve years after. Naturally, nothing can be said of the prospect of symptoms of Symphysis pericardii later in life, but it is hardly probable when they have been quite symptom-free such a long time. Presumably, therefore, it is justifiable to characterize the affection as Pericarditis sicca juvenilis benigna.

*Conclusion.* The author describes four cases of young, rapidly growing men with pericardiac friction sounds with an acute onset, but otherwise no symptoms whatever, especially no signs of infection. On account of their uniform course the author believes it justifiable to set them up as a special disease under the name of Pericarditis sicca juvenilis benigna.

## MULTIPLE JUVENILE EPIPHYSEAL CHANGES

By  
*Chr. I. Baastrup.*

A boy, of normal health till the age of 7, suddenly fell ill. His parents were abroad by that time. I have been unable to procure further information on the nature of the disease, which was diagnosed as poliomyelitis, because the boy, after the febrile period, had difficulty in using his legs correctly. Apart from these troubles the boy was healthy until a period of indisposition at the age of 9. His lungs were X-rayed. The skiagrams revealed a somewhat doubtful shadow line, because of which I found it advisable to have the boy under observation. The subsequent course gave no evidence, however, in support of the diagnosis of tuberculosis.

Pelvis and knee-joints were X-rayed, because of his difficulty in using his legs at the age of 7. The skiagrams revealed changes in the knees of the same nature as those described in the following, only far less pronounced. As they were symmetrical, and as epiphyses may have a slightly irregular character in children without this necessarily implying a pathological condition, an exact diagnosis was not ventured upon on the basis of these not very pronounced changes.

At the age of 12 the boy was submitted to another X-ray examination. He was a tall, well-shaped boy. The only extraordinary thing about him was his stiff way of running, and on the whole his peculiar way of using his legs.

X-ray of the knees showed pronounced deformation of the articular surfaces, fraying of parts of the latter with small, isolated bone particles, and slight osteosclerosis towards the joint line. The anterosuperior part of the patella was almost completely detached.

The entire skeleton was X-rayed next: The skull and the

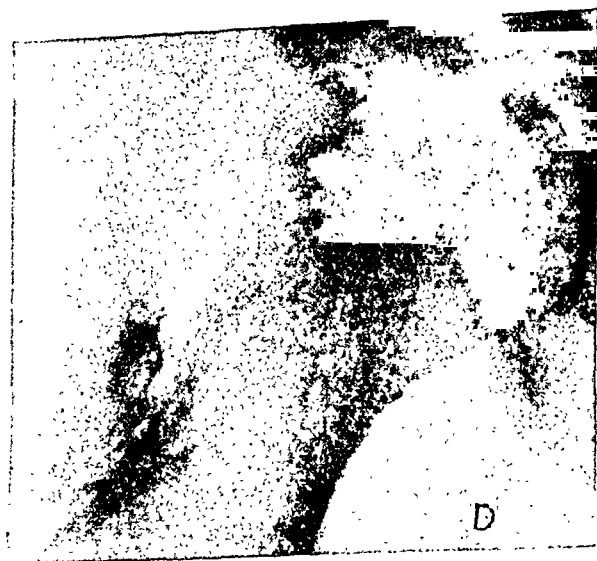


upper part of the vertebral column were judged to be normal; but the lumbar part of the column presented peculiar compact lines running parallel to the greatly corrugated upper and lower surfaces of the vertebral bodies. The shoulder areas were changed but little, whereas both elbows and the carpaer bones presented considerable changes of the same nature as those described for the knees. The metacarpal bones and the phalanges had undergone no changes worth mentioning.

Hip-joints normal. The trochanter major epiphyses presented a spongy, irregular structure. The talocrural region was slightly deformed, but the anterior portion of the tarsus and the metatarsus were greatly deformed with ossicles and Köhler-II-like changes of the articular head. The fourth and fifth metatars. bones and the distal surfaces of the second and third metatars. heads were slightly irregularly shaped, while the first presented a marked irregular shape. There were found slight changes of the interphalangeal joint of the first toe. Independent small bone fragments were seen in different places, most pronounced between the scaphoid bones and the metatarsal bones, on both sides.

The disease was entirely symmetrical. Diaphyses normal.

In March 1946 I again had occasion to X-ray examine the patient, who was now a tall, slender, normal-looking man, aged 18, who claimed complete well-being. His gait was, however, slightly waddling. Height 190 cm.



X. ray: Head normal. Vertebral column normal, except for the slightly corrugated outlines of the upper and lower surfaces of the bodies of the lumbar vertebrae. Shoulder-joints normal. Inconsiderable changes in the elbows, where the right articular head presents a slightly irregular outline, while the left looks normal. The ulnar styloid processes are very coarse, but otherwise both wrists, hands, and fingers look normal.

Hip-joints normal. The articular surfaces of the knee-joints are somewhat corrugated medially, and there is slight osteophyte formation along the upper border of the patella. Ankle-joints and wrists normal. Metatarsal bones and phalanges present nothing abnormal, except for flattening of the distal articular surface of the head of the fifth metatarsal bone on both sides.

The so-called osteochondrodystrophies constitute a polymorphous group of diseases, which the various writers have tried to systematize. No agreement has been obtained so far, not even with regard to the nomenclature. Schinz (1939) divides the diseases belonging here in the following groups: 1) avitaminotic (rickets, osteomalacia, Barlow's disease, and sprue), 2) hormonal (acromegaly, cretinism, etc.), 3) growth diseases (dwarfism, gigantism, etc.), 4) hereditary diseases (17 groups among which chondrodystrophy, osteogenesis imperfecta, and Ribbing's disease), and 5) aseptic epiphyseal necroses.



The system set up in 1937 by Jaffe-Hirsch seems clearer, at least to the describing radiologist:

A. Localized osteochondrodystrophy

- 1) localized in one epiphysis (e. g. Calvé-Perthes' disease)
- 2) — in one bone (e. g. Köhler I)
- 3) — in a few epiphyses (e. g. Thiemann's disease)

B. Generalized osteochondrodystrophy

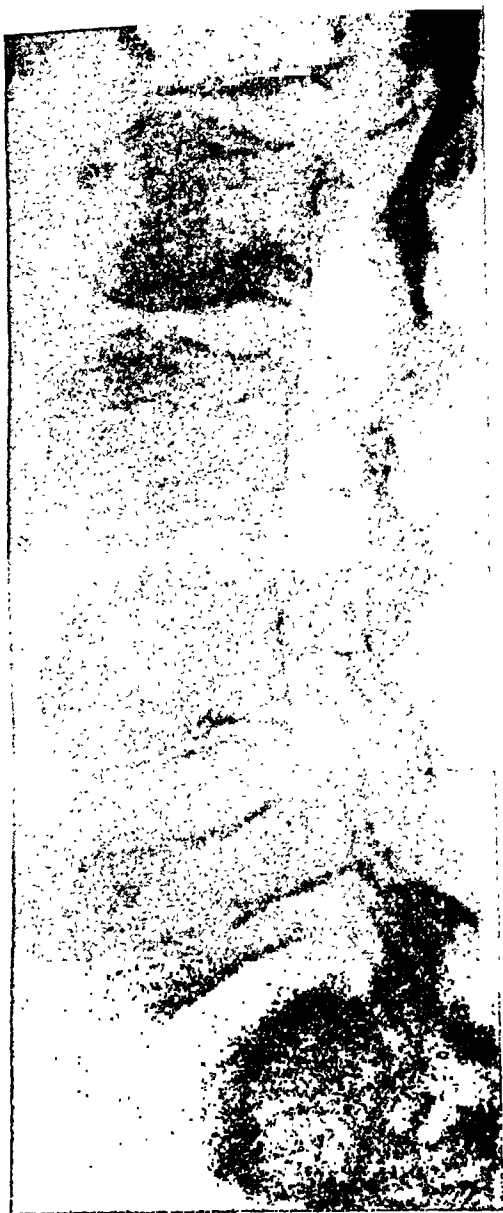
- 1) achondroplasia
- 2) dyschondroplasia (multiple chondromas)
- 3) eccentrochondroplasia.

"Eccentro" means that the development occurs from multiple ossification nuclei, and not from a single one.

Silfverskiöld (1925—6) has described an osteodystrophy in mother and son where the epiphyseal cartilage was deformed and the ossification irregular. He called the cases *formes frustes* of chondrodystrophy with malacic osseous changes.

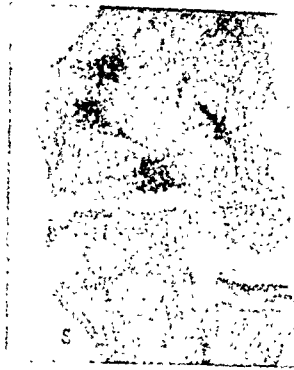
Grudzinski (1928) mentioned 3 atypical forms of achondroplasia: 1) partial, 2) abortive, and 3) clinically variable. He placed "Silfverskiöld's multiple osteochondropathy" in the last group.

In 1929 Morquio published a description of a sibship of 5, of whom 4 presented a similar pathological condition. The parents were first cousins.



Changes of the above nature have since commonly been designated as "Silfverskiöld-Morquio's disease" or "Morquio's disease". Numerous reports have been published since on this pathological condition, but nearly all the writers mention cases from one family group only.

J. F. Brailsford (1928—9) uses the term chondro-osteo-dystrophy for a number of diseases ranging from cases so light that they are hardly noticed, by all degrees up to cases so severe



that the individuals concerned cannot survive. Some cases develop in infants, who present nothing abnormal during the first months or year. The changes are characterized by irregular growth of the epiphyses, and by the fact that both primary and secondary ossification centres are involved. Most pronounced are the changes in the vertebral column, where kyphosis is of frequent occurrence, and the final result is development of very low-shaped individuals, even dwarfs. A second group presents changes in the diaphyses resulting in abnormally short extremities. In a third group the disease is localized in the vertebral column and the hip-joints, more rarely the knee-joints. In a fourth group there are found changes in the column only.

Ribbing describes a family in which various members presented changes very similar to those observed in the present case, only with Calvé-Perthes-like deformity of the hip-joint as well. Ribbing made reflections on the differentiation between Silfverskiöld-Morquio's disease, Kaschin-Beck's disease, and the changes in cretinism, among others, which, however, lie outside the scope of the present work, but which are concerned chiefly with the conditions of the diaphyses.

This large, heterogeneous group of diseases is characterized by the following common features:

- 1) Familial occurrence demonstrated in practically all cases.
- 2) Nanism, or at least reduced stature.

3) Epiphyseal changes.

4) In many patients absence of the femoral head; in Ribbing's cases Calvé-Perthes-like changes of the femoral head.

In attempting to rubricate the present case within this polymorphous group of diseases one is struck by the fact that, although the epiphyseal lesion bears a close resemblance to the generally known local aseptic juvenile epiphyseal changes, the localisations differ very much from the classical ones. There were found neither Calvé-Perthes' nor Schlatter's changes, no more than Köhler I and Köhler II changes of the second metatarsal bone (but Köhler-II-like changes of the fourth and fifth metatarsal bones, which are not typical, however). Kienböck's lunatummalacia was not observed, neither were Scheuerman's vertebral bodies (which many doctors, no doubt unjustly, regard as belonging to this group of diseases). Thiemann's disease is multiple, and similar changes were perhaps traceable in the bones of the hands of my patient, and they were markedly present in the bones of the feet. However, Thiemann's disease attacks only hands and feet.

The present case also resembles group 3) of the generalizing forms of osteochondrodystrophy, i.e. that of "eccentrochondroplasia" with regard to the epiphyseal changes; but the parents are not related, and familial occurrence of the disease has not been demonstrable (the patient's father is a greatly esteemed physician, whose statement of lacking familial occurrence must therefore be regarded as fully reliable). There is no question at all of nanism. The patient measures 190 cm., and his two siblings 188 and 190 cm. respectively, in other words very tall people. Finally the hip-joints presented no unquestionable abnormality.

As the disease seemed extremely difficult to rubricate, and as I had no access to the literature from the past 7 years, I conferred with Ribbing, whom, on account of his studies, I took to be particularly conversant with these questions. Ribbing would not acknowledge the case as one of Ribbing's disease because of the lacking familial occurrence. I sent the skiagrams to Brailsford, who must be regarded as the greatest authority

within this field at present. Brailsford supposed the disease to be a light form of chondro-osteo-dystrophy. I am much obliged to both these experts for their help.

*Summary.*

A description is given of a non-familial case of multiple epiphyseal changes, which differ on various points from the cases of a related nature reported in the literature.

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## PROGNOSIS AND TREATMENT OF MASSIVE HAEMORRHAGE FROM GASTRIC AND DUODENAL ULCERS

By  
*Erik D. Bartels, M. D.*

The treatment, both the dietetic and the operative, of massive haemorrhage from gastric or duodenal ulcers has been a subject for much discussion of late years.

As to the dietetic treatment Meulengracht claims to have obtained excellent results by giving the patients ample food in purée form from the very beginning. He is, besides, of the opinion that the lethality is reduced very considerably. There seems to be general agreement on the fact that inanition and desiccation are harmful to these patients, who are deficient in protein and often in a state of shock. But the immediate treatment with purée diet is by various writers regarded as too radical. They prefer a slightly extended Faber-Sippy's diet, as in other cases of ulceration (Bockus), partly because a number of bleeding patients have dyspepsia as well and partly because many patients have difficulty in eating solid food immediately after the haemorrhage. Most writers recommend in addition transfusions acc. to requirement.

It is difficult to make out from the literature whether the prognosis *quoad vitam* is improved by Meulengracht's diet. Meulengracht himself has obtained a lethality of 1 %. Clemmensen & Lund, for instance, found it to be 3.8 % on the same diet, but without transfusions (7 % if, like Meulengracht, they included complicated cases), and Christiansen 7.9 % in a series treated by inanition and with morphine. Foreign lethality statistics present even greater differences (Bockus). This may be due to the method of treatment, but other possibilities are conceivable: 1) Change in character of ulceration. Duodenal

ulcers are now more frequent than previously, and they more rarely involve life-threatening haemorrhage than the gastric ulcers. 2) Increase in number of hospitalized patients, notably in countries with a well-developed national health service. Previously only severe cases of gastric haemorrhage were admitted, but now also most of the light ones, which were formerly treated at home. Thus in Copenhagen, for instance, the absolute number of fatal bleeding peptic ulcers in the hospitals seems to remain at a constant level, whereas the relative number is falling (J. L. Hansen, J. L. Hansen & J. Pedersen). Hence two series are comparable only if derived from the same place and period.

3) The series of cases may present other differences. Meulengracht had only one death within the first 24 hours, against more than one-third of ours within this period. Association with other diseases plays a great part, and where these are not absolutely fatal it may be a matter of judgement whether the patient should be included. In this connection mention should be made of the patients who on X-ray examination after completed treatment present neither niche nor deformation indicative of an ulcer. Such patients constitute one-third of Meulengracht's series and one-fourth of ours. They are generally taken to have had superficial erosions, which had healed up. However, occasionally the disease is only a severe gastritis with a tendency to haemorrhage. This is known to be true, because some such cases end fatally. Two cases were observed in Dept. B in the course of 1946.

Man, aged 65. Tetanus in 1916. Since 1940 progressive paralysis agitans. Has to be helped with everything. Gets scopolamine. Never dyspepsia except for some constipation. The day before admission two large coffee-ground vomits (ab. 2 litres). In the Dept. first alimentary vomits, then hiccup, and finally minor coffee-ground vomits. Faeces not black, but presented strong benzidine reaction. Died the second day. Necropsy: Mucous membrane of stomach and small intestine, notably the ileum injected by numerous minor haemorrhages. No ulceration, no tumour. Peritoneum slightly injected. Brain: no visible abnorm.

Man, aged 62. Insulin-treated diabetes since 1932. Arteriosclerotic. In 1944 cerebral thrombosis. Admitted with pneumonia and serous pleurisy, cured by lucosil and penicillin. Had been up and about for a few days when one night he got a profuse, fresh

haematemesis and died within 2 hours. Necropsy: Stomach blood-filled. Acute and chronic inflammation of the mucous membrane, but no erosions. No other demonstrable cause of haemorrhage in gastro-intestinal or respiratory passages. Pronounced arteriosclerosis of coronary arteries and aorta. Myocardial fibrosis.

This is another type of haemorrhage than that seen in callous ulcer with arrosion of an artery. Krarup found that the bleeding ulcer has a better prognosis after the first attack than the painful ulcer, no doubt because the group of painful ulcers contains exclusively patients with X-ray verified sore, whereas that of bleeding ulcers comprises many patients (perhaps 20 to 30 %) with only gastritis. The lethality rate depends, therefore, to a great extent on the proportion of this type of patients in a series.

The age incidence plays an even greater part. The older the patients the higher the lethality. American writers draw the line between good and bad prognosis at 45 years of age, which is perhaps a little early. The risk increases substantially between the ages of 50 and 60. It is considerable after the age of 60 and very great after the age of 70. It is difficult to indicate definite figures. Under 50 years of age the relative magnitude is 1 % and over 70 years 30 %, when complicated cases are included. There are various reasons for this difference: 1) The ulcers become bigger and deeper with increasing age, thus causing arrosion of larger arteries in the gastric wall or adjacent organs (pancreas). 2) Old vessels become indurated and arteriosclerotic, thus having greater difficulty in closing than young and elastic arteries. 3) Haemorrhagic shock is worse for old people. 4) The incidence of complications increases with increasing age.

Here we come to the other cardinal problem in the discussion on the treatment: Should operation be undertaken in the cases where the bleeding does not stop spontaneously? In America Finsterer, among others, has gone in for operation within 48 hours of all bleeding ulcers, because they may as well belong to the severe cases. The lethality increases very considerably if this time limit is passed. Among the Scandinavian writers Bohmansson originally advocated operation. Later on he modified this radical view, however, being now of the opinion that

a bleeding ulcer should generally be treated conservatively according to Meulengracht's method, and only in certain cases submitted to operation. The lethality of haemorrhage cases among patients under 50 being ab. 1 %, or about the ordinary laparotomy lethality, these patients should on principle be treated conservatively and only rarely be operated on. The discussion may therefore be limited to comprising middle-aged and elderly people.

### *Own Series of Cases.*

The author's reason for desiring to contribute his share to the discussion is the fact that within the period January-February 1947 there occurred 4 deaths after bleeding ulcer in the K.A.S.G., Dept. B, where also elderly patients have so far been treated conservatively. All the cases of death of individuals over 15 after haematemesis and melaena in the three Med. Depts. B, C, and F<sup>1)</sup> from Jan. 1, 1945 to Febr. 28, 1947 were studied together with the deaths due to bleeding ulcer in Dept. F from Jan. 1, 1938 and in the two others from Jan. 1, 1939. By haematemesis is understood vomiting of large amounts of fresh or stale blood, and by melaena passage of pitchy stools.

### *Haematemesis and Melaena (all causes).*

31 patients presenting one or both phenomena have died in these departments since Jan. 1, 1945. 16 were admitted on these diagnoses alone and 8 on these diagnoses, but also gastric ulcer (3), cancer (3), hepatitis (1), and jaundice (1). In 7 cases the haemorrhage occurred after the admission. The ages ranged from 40 to 85; only 5 were under 60. The patients were thus chiefly elderly or old people. In 4 cases no post-mortem examination was made, but in 3 of these the diagnosis was otherwise verified. Only 1 case, diagnosed as gastric cancer, is perhaps a little doubtful. The verified diagnoses were as follows:

Gastric or duodenal ulcer: 12.

Gastritis without demonstrable erosions: 2.

Gastric, oesophageal, or duodenal cancer: 10.

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<sup>1)</sup> I wish to thank the chiefs of the departments M. Siggaard Andersen, M. D., and F. Wulff, M. D., for permission to use their cases.

Epid. hepatitis w. cirrhosis and oesophageal varices: 6.

Haem. diathesis (bone marrow destruction at c. metastases): 1.

The 3 most common causes of haemorrhage are represented, viz. ulcer, cancer, and oesophageal varices. Haemorrhagic diathesis is here the only representative of the rarer causes. Many others are mentioned in the literature: deficiency of prothrombin in jaundice, lesions of spleen and portal veins (in particular Banti's syndrome), diaphragmatic hernia, benign gastric tumours, haemorrhages from bile ducts, and ruptured aortic aneurism. To these may be added the false haematemeses of swallowed blood.

The differential diagnosis is often difficult directly on admission because of the poor state of the patients, which precludes close questioning and examination. To elucidate the source of error it has been examined, as far as possible on the basis of the case records, how often the diagnosis of ulcer or no ulcer made within the first 24 hours held good on subsequent examination.

Diagnosis within the first 24 hours.	Verified diagnosis.
Ulcer: 13 .....	Ulcer: 8
	Not ulcer: 5
Not ulcer: 18 .....	Ulcer: 4
	Not ulcer: 14

In 22 cases the first diagnosis was correct and in 9 wrong. Of the 5 cases in which the necropsy revealed other findings than ulcer 2 were diagnosed as hepatic cirrhosis, 1 as gastritis, 1 as gastric cancer, and 1 as duodenal cancer.

In the latter case (a man, aged 72) a duodenal ulcer had been ascertained by X-ray 4 years previously. The profuse haemorrhages stopped after repeated blood transfusion, but the patient developed hepatic tumour and jaundice, and died.

The 4 cases in which the mistaken diagnosis tended in the opposite direction are of the greatest practical importance. In the first case the diagnosis was one of obs. for uraemia.

Woman, aged 72. Admitted unconscious with deficient data. Dyspepsia for 2 years with acid and often slightly bloody vomits and frequently black stools. Great loss of weight. The last 2 days bloody vomits. On admission small, coffee-ground vomit. Faeces not black, but with pos. bz. reaction. Pulse regular and full. Hb: 75 %.

Blood urea 124 mg. %. Died after a few hours. Necropsy: Large, callous, pyloric ulcer with open artery. Moderate coronary sclerosis.

The other patient had acute hepatitis, and the haemorrhage was thought to be due to hypothrombinaemia, possibly combined with hypoproteinaemia.

Woman, aged 40. Never previously dyspepsia. For the past month tiredness, anorexia, and nausea. Admitted with severe hepatitis; icteric index: 150. The following day haematemesis. Blood transfusion and vitamin K with no effect. Was feeling very bad; smelled of liver. Takata-Ara reaction highly pathological. Prothrombin 50 % Died within 24 hours of admission. Necropsy: Superficial duodenal ulcer with open artery. Pronounced, sub-chronic hepatitis.

Such diagnostic mistakes are difficult to avoid. The two remaining cases (woman aged 77 and man aged 72) are instances of the most common mistake, i. e. that of too often regarding dyspepsia in old people as a sign of cancer (cf. J. L. Hansen), particularly when recently developed. 7 of the present ulcer patients over 65 had had no dyspepsia whatever till the last month before the haemorrhage. Life-threatening haemorrhage from the gastro-intestinal canal should, therefore, be regarded as due to a benign disease and treated accordingly until the reverse has been proved.

The differential diagnosis is not easy in these cases and may occasionally be made only by X-ray examination which is also necessary for localisation of the ulcer in case operation is contemplated. Bohmansson states that cautious X-ray examination is harmless even at the acute stage. The above case of duodenal cancer shows that the examination must be recently made to be of any value.

#### *Deaths Due to Bleeding Peptic Ulcers.*

From Jan. 1, 1939 to Febr. 28, 1947 there were 31 deaths due to bleeding peptic ulcers and 2 to gastritis with haemorrhage in the Medical Departments of the K.A.S.G. To these may be added 3 cases from 1938 in Dept. F. The card index allowed the lethality to be calculated only from Jan. 1, 1945.

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Age	Bleed-ulcer	Deaths	%	X-ray No abn.	Deaths	%	All haem.	Deaths	%
15—49 ..	75	1	1,3	23	0	0	98	1	1,0
50—59 ..	30	1	3,3	11	0	0	41	1	2,4
60—69 ..	26	3	11,5	6	2	33,3	32	5	15,6
70— ..	18	7	38,9	9	0	0	27	7	25,6
All ages .	148	12	8,1	49	2	4,0	198	14	7,1

The lethality rate was rather high; but no cases, even the most complicated, were omitted, and the two first months of 1947 brought the 4 deaths in Dept. B alone, which occasioned the present investigation. Between Jan. 1, 1945 and Febr. 28, 1947 such deaths averaged 6.5 yearly, while between Jan. 1, 1939 and Febr. 28, 1947 there were 33 such deaths, or an average of 4.0 yearly. If we take the number of patients admitted with bleeding peptic ulcer to be fairly constant through the entire period, these figures correspond to a lethality of 4.5 %, which is rather lower than that found by Clemmesen & Lund.

32 (plus 2 gastritis patients) died of the haemorrhage. The latter was stopped in the two latter patients; but one, who was suffering from a severe myocardial degeneration with angina pectoris, developed pulmonary embolism in connection with a bath, while the other, suffering from nephrosclerosis, developed uraemia.

24 (plus 2 gastritis patients) were men and 10 women.

The age incidence was as follows:

	Ulcer	Gastritis
15—49:	2	0
50—59:	8	0
60—69:	8	2
70— :	16	0

Nearly half were over 70 and more than two-thirds over 60. The fact that equally many died between 50 and 60 and between 60 and 70 goes to show, however, that the danger zone begins about the age of 50.

With a view to the possibility that some of these patients might have been saved by operation they were all divided in 3 groups according to clinical finding, and particularly post-mortem finding.

A. 16 patients for whom operation would have involved a very great risk.

7 were over 75 years of age and presented pulm. cancer (1), severe arteriosclerosis plus nephrosclerosis (2), severe arteriosclerosis plus myocardial affection (2), hypertension plus pyonephrosis (1), and hepatic cirrhosis (1). 4 men between 70 and 74 were suffering from cavernous pulm. tub. (1), hepatic cirrhosis (1), hepatic cirrhosis plus diabetes mellitus (1), and hepatic cirrhosis plus myocardial fibrosis (1). A woman, aged 66, presented inoperable mammary cancer plus meningeoma in the right hemisphere. 2 men between 60 and 70 had pneumonia plus stenosis of the aortic valve (1) and myocardial deg. plus excessive adiposity (1). A woman, aged 54, had mitral stenosis causing symptoms, and a woman, aged 40, severe subchron. hepatitis. (The 2 gastritis patients both had severe complicating diseases, as mentioned before).

B. 6 patients with less severe complications, but still with rather small chances of surviving a great operation.

1 otherwise normal patient was 79 years old. 3 between 70 and 74 had rather pronounced coronary sclerosis, 1, aged 73 severe prostatic hypertrophy, and a 57-year-old man very considerable coronary sclerosis.

C. 10 patients (9 submitted to post-mortem examination and 1 not) who presented no complications and where the post-mortem examinations revealed large, callous ulcers with open arteries. The ages ranged between 40 and 69. 9 were over 50. 3 died the first day, 1 the second, and 6 lived up to 9 days. One cannot divest oneself of the idea that some of these patients might have been saved by surgical intervention, if they had been distinguished in due time partly from those in whom there occurs spontaneous haemostasis, and partly from those whose complications preclude operation.

Before passing on to a further discussion on how to make such a distinction there is reason to discuss three facts of importance where the problems of treatment are concerned.

1. *The chance of spontaneous haemostasis if the patient could be kept alive for a longer time.*

Haemostasis occurred in 2 of the 34 patients with a bleeding peptic ulcer. One was submitted to post-mortem examination

and presented a long-existing, callous ulcer with no visible arterial lumen. 2 were not examined after death. In 3 patients, of whom 2 died the first day and 1 the second, the haemorrhage came from fresh erosions in a gastritis. These could no doubt have been healed if the patients had been able to survive the first few days. In the two gastritis cases there should also have been a chance of spontaneous haemostasis. The remaining 27 patients presented long-existing, callous ulcers, in nearly all cases with open, coarse, and indurated arteries. The immediate impression was one of little chance of closure in these cases.

22 of the ulcer patients and the 2 gastritis patients had never bled before, while 12 ulcer patients had had one or more haemorrhages. If the haemorrhage had come from the same ulcer each time there might perhaps after all have been a chance of spontaneous haemostasis. Nothing certain can be said, however, the more so because 10 patients had multiple ulcers. The chance of spontaneous haemostasis in these cases must thus be regarded as very small.

## 2. *Would a change of diet have improved the result?*

The effect of a certain diet does not manifest itself till after some days. The deaths of the 34 patients who died of the haemorrhage occurred as follows:

1st day:	14
2nd—3rd day:	8
4th—9th day:	11
26th day:	1

The majority of such patients having a poor appetite those who died within the first 3 days must be supposed to have been inaffectible by the diet. The same may have been the case with some of those who lived a little longer. Hence, dietetic measures are hardly likely to have played any part for the prognosis in the present series.

The question of the importance of the diet can furthermore be elucidated by a comparison between the results from Dept. B and Dept. C. Dept. B used treatment according to Faber beginning with the diet of the 3rd week, i.e. custard and semoule gruel, while Dept. C used Meulengracht's diet (Dept. F changed its treatment in the course of the period). The remaining treat-

ment, including the indications for blood transfusion, seems to have been the same.

Died of haemorrhage (ulcer and gastritis).		
	0—1 day	2—26 days
Dept. B: . . . . .	5 (+ 2)	4 (+ 2)
Dept. C: . . . . .	5	4

If we leave out of account the fatal cases of bleeding peptic ulcer accumulated in Dept. B within the first two months of 1947 (bracketed figures) the numbers of deaths are exactly the same in the two departments. If they are included the figures are shifted slightly in favour of Meulengracht's treatment. The figures are, however, too small to allow of definite conclusions. In other words, the present series gives no evidence to suggest that the *purée* diet should be superior to the ordinary ulcer diet from a life-saving point of view in cases of bleeding ulcer. It should be emphasized, however, that the patients in Dept. B are never treated by inanition.

### 3. Which is the direct cause of death in these cases?

Some of the patients who die of the haemorrhage are already suffering from diseases so severe that even a small trauma may kill them. The haemorrhage need not be particularly profuse, and the main cause of death is actually the disease regarded as the complication (coronary sclerosis, etc.).

This is not the general rule, however. The majority present either at once or after renewed haemorrhage the clinical picture of palor, exhaustion increasing to loss of consciousness, low blood pressure, and small, quick, and soft pulse. They complain of tiredness, weakness, dyspnoea, headache of a throbbing character, and ringing in the ears. Renewed haemorrhage is often followed by syncope. The haemoglobin values are fluctuating. The lowest blood per cent values ranged in the present series between 33 % and 110 %. The figures are of little interest, because a balance between plasma and blood cells is rarely attained before death; but they are suggestive that the decisive factor in the picture is not a direct haemoglobin deficiency. The rise often observed in blood urea points in the same direction.

It has been suggested that it should be due to resorbed blood (Clausen), but a quantitative study of the protein concentration in a few litres of blood renders this an unlikely theory. It is more reasonable to correlate the sign with the clinical picture and the haemoglobin values and conclude that the patients are suffering from acute haemorrhagic shock with the usual sequelae. If there have been periods of vomiting or desiccation of the patient due to protracted shock and reduced intake of fluid there is seen also disturbances in the acid-base equilibrium as well as hypochloraemia. A blood transfusion of 500 c.cm. often leads to improvement of the general state, which does not depend on the rise obtained in the haemoglobin value.

We have, therefore, more and more become alive to the fact that the patients are shocked, and it is advised not to let them lie in protracted shock, which may involve renal lesion and uraemia. During the war, when the possibility of procuring blood for transfusion was increased, some British writers tried to give heroic transfusions in these cases (up to  $1\frac{1}{2}$  to 2 litres daily, a total of 10 to 15 litres to a few patients) with excellent results. The series comprised, indeed, only 30 cases varying greatly in intensity with 1 death; but still they showed that the patients can be restored within a very short time and that there is no need to fear that the transfusions should intensify the haemorrhage. On the contrary there soon occurred haemostasis in 29 of the cases. Care was always taken that the blood was infused at such a rate that sudden, violent rises in blood pressure were avoided. Whole blood or concentrated blood cell suspensions are in such cases more rational than plasm, since there is a considerable loss of blood cells at the same time.

The conclusion is then that a great number of haematemesis-melaena patients die of haemorrhagic shock and that the treatment should in the first instance aim at eliminating the shock. Frequent and large blood transfusions can be given without preventing the haemostasis. The electrolyte and fluid balances must be controlled at the same time in the usual surgical manner and saline possibly added subcutaneously. The risk involved by inanition may be naturally explained by the fact that the patient is supposed to be deficient in protein, electrolyte, and fluid.

## *Arrangement of Treatment of Patients with Haematemesis and Melaena.*

The results arrived at on the basis of the present series of cases seem to warrant the following conclusions: The treatment of acute gastric haemorrhage should in the first instance be one of rest, confinement to bed, and from the very beginning a diet rich in protein and fluid, the form of which is of minor importance. The first few days one should be on the lookout for shock symptoms and, if such occur, give large and frequent blood transfusions as well as morphine acc. to requirement. The salt and electrolyte balances should be carefully watched. Moreover, it is essential that the exact cause of the haemorrhage and the severity of possible complications be ascertained as soon as possible.

If the diagnosis is one of gastric or duodenal ulcer and profuse haemorrhage persists for more than 36 to 48 hours in patients without severe complications, X-ray examination should be made and operation considered, particularly where patients between the ages of 50 and 70 are concerned. In younger patients the haemorrhage will nearly always stop spontaneously.

The author is of the opinion that ab. one-third of the patients in the present series might perhaps have been saved if the above principles had been carried through. In a few cases treatment of the shock would have involved a chance of spontaneous haemostasis (a few patients with oesophageal varices, e.g. in Banti's disease, may possibly have the same chance), and in others it would have made operation possible. The remaining two-thirds were so ill from other diseases that they would have died in any case.

### *Summary.*

31 cases of fatal haematemesis and melaena from all causes and 34 cases of fatal bleeding from gastric or duodenal ulcer or gastritis are studied. The following conclusions are drawn.

1. The differential diagnosis may be difficult on admission. The patients therefore shall always be treated as having a benign disease until the reverse is proved.
2. In patients under 50 bleeding ulcer very seldom leads to death, in patients over 60 much more often.

3. About two-thirds of the patients die because of complications. Probably no treatment will be able to save them. Among the remaining one-third some could probably be saved if extensive blood-transfusions and perhaps surgery were used.

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While this paper was under press Meulengracht in the *Arch. Int. Med.* (Dec. 1947) has published his experiences with 26 cases of dead from bleeding ulcer. He arrives at practically the same conclusions as mentioned above.

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## SPLENIC NEUTRO-THROMBOPENIA

By

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That the function of the spleen in some way or other has an influence on the hemopoiesis in the bone marrow seems beyond doubt, but by exactly what process this "splenogenic marrow effect" is brought about is less clear. In certain types of anemia (erythrocytopenia), neutropenia or thrombocytopenia as isolated or combined phenomena, a splenectomy will cause an increase in the number of the involved cells in the blood. The increase may be temporary or permanent, and may reach both normal and supernormal values. In many of these cases there will be histologically demonstrable changes in the spleen, but in some it has not been possible to demonstrate anything abnormal. The changes may be secondary in relation to various well defined pathologic conditions (Hodgkin's disease, tuberculosis, sarcoidosis, etc.), but in others it may possibly be a question of primary affection of the reticulo-endothelial tissue, perhaps localised to the spleen alone.

It is generally supposed that the spleen exercises an inhibiting influence on the cell-production in the bone marrow either in the manner that the maturation of the cells in the marrow is retarded («maturation arrest») or that their emission into the blood stream is delayed; — or perhaps the inhibition acts in both these directions. Under certain pathologic conditions this inhibitory function is increased, and the result becomes a deficiency of cells in the peripheral blood (hypersplenism; cf. Dameshek). Doan & Wiseman explain some of these conditions as directly caused by a process in the spleen, because they in the latter found larger quantities of phagocytic cells than normal, whereby the cell destruction is increased, re-

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sulting in a deficiency of cells in the blood. A new explanation, suggested by Johansen, is based on the theory that the spleen normally regulates the supply of a substance necessary for the maturation of the cells. By absorbing this substance to a greater or lesser extent from the blood, the spleen should be able to exercise a regulating influence on the hemopoiesis in the marrow. Under certain pathologic conditions the absorption should be greater than normal and the marrow thus be deprived of this substance, with the result that the maturation in the marrow is inhibited and the blood stream becomes deficient in cells.

None of these theories can, however, explain why this inhibitory action in some cases is selective, affecting either the erythropoiesis, the granulopoiesis or the thrombopoiesis, and in other cases affects them more or less combined, with the extreme result that there in the circulating blood is a deficiency of all the cells derived from the bone marrow. It would therefore be extremely interesting if it was possible to demonstrate a histologic distinction between particular changes in the spleen corresponding to the different types of splenogenic inhibition in the marrow. With the present knowledge there does not seem to be any basis for such a distinction. Altogether the interaction between the spleen and the bone marrow presents so many pathophysiologically interesting problems that any case reports contributing to their elucidation will be justified. Besides, it does not seem that the existence of these splenogenic inhibition syndromes is generally recognised, and many patients therefore go about with their invalidating symptoms though they in many cases might be cured, or at least symptomatically cured, by splenectomy. The following is a report of such a case of chronic neutro-thrombopenia where the symptoms made the patient more or less of an invalid, and in which splenectomy was performed with the result that he now for over two years has been completely free from symptoms, even though the hematologic conditions have not become entirely normal.

#### *Case Report.*

The patient, a married waiter aged 25, was referred to the Radium Center for Jutland on September 15, 1944, for chronic

Table 1.

Year Date	1943	1944			
	Jan. 14	Sept. 16	Okt. 9	Novb. 23	Febr. 1
Sed. rate mm/hour ....		4	5	7	4
Hb. % .....		106	83	85	85
Erythrocytes .....	5.39	4.57	3.79	4.05	4.00
Leukocytes .....	3.000	1.100	1.200	1.160	760
Platelets .....	10.100	12.000	50.000	28.000	65.000
Neutrophils % .....	29	10	34	24	20
— total .....	870	110	408	278	152
Eosinophils .....	3	22	26	8	16
Lymphocytes .....	62	30	20	52	56
Monocytes .....	6	38	20	16	8

neutrothrombopenia (Record no. 2407/44). He stated that since his earliest infancy he had suffered from severe nosebleeds, which would start spontaneously, often in periods, sometimes lasting only a short while, at other times for several days. He also had a tendency to get "blue spots", even by the slightest trauma. As far back as he remembered, he had suffered from frequent, rather severe inflammations of the throat, stomatitis and gingivitis, with bleeding, foul-smelling gums, often accompanied by rises in temperature. He had been several times in hospitals for these troubles, since 1940 five times. On two of these occasions, in 1940 and 1944, he had been in the Municipal Hospital in Horsens, where a *granulocytopenia* and *thrombopenia* combined with a "maturation arrest" of the granulopoiesis in the sternal marrow was demonstrated. In the intervals between the acute exacerbations he had had periods of great fatigue. Altogether, fatigue had been a dominating symptom as far back as he remembered. In the last years he had been a waiter by profession, but the frequent attacks of stomatitis, with foul breath, and the spontaneous nosebleeds, which were liable to start while he was serving the guests, together with the fatigue, had made it impossible for him to attend to his work. He had been treated with blood transfusions, ascorbic acid, roborants and disinfection of the mouth, but all without the slightest effect.

When he was admitted to the Radium Center his appearance was that of a well-proportioned, though rather thin young man and corresponded to his age of 25 years; but he looked tired and overworked, his face was pale and there were dark shadows under the eyes. The mucosæ were not markedly anemic, though, and there was no icterus. There were small petechiæ all over the trunk and extremities. Otherwise the physical examination showed nothing abnormal about the eyes and ears. The teeth were somewhat carious, but at the time there was no stomatitis or gingivitis,

Splenectomy	1945					1946	1946	
	Febr. 2	Febr. 3	Febr. 5	Febr. 15	April 8	Aug. 4	June 19	April 9
		10	34	17	4	4	2	1
		95	98	96	90	109	87	106
		5.02	4.78	4.73	4.41	4.36	4.57	4.96
		8.300	4.700	4.600	4.700	4.500	4.600	3.800
		250.000	320.000	400.000	400.000	200.000	80.000	300.000
		68	58	54	21	26	29	38
		5.644	2.726	2.484	987	1.190	1.330	1.440
		0	8	6	2	17	8	5
		8	8	14	66	44	44	44
		24	26	26	11	13	19	13

nor anything abnormal in the fauces. Near the angle of the jaw on both sides a couple of hazelnut-sized, freely displaceable, slightly tender lymph nodes could be felt, but otherwise there was no peripheral lymph node tumor. Stethoscopy of heart and lung normal. The abdomen soft and not tender to pressure. No tumors were felt, nor any enlargement of the liver or spleen.

Psychically, the patient was very labile. He was greatly depressed by his chronic disease and his resulting economic worries. Otherwise his principal complaint at the time was a feeling of overwhelming fatigue.

A number of examinations were made; the results of the most important blood examinations are shown in Table 1. It will be seen that the hemoglobin percent and erythrocyte values were normal, while there was marked leukopenia and thrombopenia. The neutropenia was due chiefly to a deficiency of neutrophils. The remarkably high monocyte count is to some extent a relative phenomenon, but at all the examinations monocytes were abundant, though always of a typically mature type. There were no immature leukocytes in the blood, and no nucleated red cells. The sternal punctate was rich in cells. The granulopoiesis especially was lively and showed marked shift to the left, with almost entire absence of the most mature forms. Megacaryocytes (and blasts) were present in the ratio of about 20 to each 1,000 of nucleated red cells, and were thus abundant. Also in the megacaryocytopoiesis there was a distinct shift to the left. The formation of platelets from the megacaryocytes was very sparse, only about 15 per cent of them showing any platelet production, and then in small numbers. The fragility of the red blood corpuscles was normal.

Of the other laboratory examinations may be mentioned that the serum protein constituted, in all, 6.2 per cent, 4.6 per cent of which were albumen, 1.6 per cent globulin. The prothrombine time and the reticulocyte value were normal, serum calcium 9.8 mg.

per cent. Tuberculin test and Wassermann negative, blood pressure 125/75.

As the blood picture was judged to be due to splenogenic marrow inhibition, it was tried, as a matter of experiment, if it could be influenced by roentgenologic treatment of the spleen, and from September 29th to October 7th 1,000 r altogether were given over the splenic region in daily doses of 100 r (factors operated with: 160 kv., 4 ma., filter 1 mm. Cu., distance 40 cm.). The treatment caused no discomfort, but had apparently no effect on the hematologic state. Neither did a series of intramuscular injections of pentonucleotide (Smith, Kline & French Laboratory, Philadelphia) in doses of 10 ml. daily seem to have any effect whatever on the granulocyte values. Personal reasons made it necessary for the patient to leave, but in November same year he was re-admitted, and examinations of the blood and marrow showed the conditions more or less the same as before (Table 1). At entrance he was in a rather poor state, with temperature 39.2° C. His breath was very foul and the gums swollen, bleeding and covered with dirty, ragged, necrotic false membranes. Under treatment with blood transfusion and alfasol the temperature rapidly went down and the oral cavity gradually became clean. The physical examination otherwise showed nothing new since his former admission. As his disease in fact made him invalid, he was advised to undergo a splenectomy, to which he consented; and on February 2, 1945, laparotomy cum splenectomy was performed (Prof. Aage Nielsen, surg. service, Aarhus Municipal Hospital). There were no complications, and the postoperative course was uneventful.

The spleen was slightly enlarged (300 g.), its surface smooth and natural, the section surface likewise. Histologic examination of sections from different parts all showed the same picture: the structure preserved, the follicles lying rather scattered and far apart. In the pulpa there was a moderate but distinct increase of the reticular cells and slight fibrosis, but no signs of excessive blood destruction, phagocytosis or pigment deposits. In the center of the follicles there was in many places a slight increase of the large, light reticulum cells, and also in the periphery of the follicles there were in a few places seen small islands of reticulum cells, often in the vicinity of a vessel. There was nowhere extramedullary myelopoiesis, but slight, diffuse eosinophilia.

After the operation there was, as seen in the Tables (1), an almost immediate rise in the granulocyte and thrombocyte values. An examination of the bone marrow shortly after the operation showed entirely altered conditions. The shift to the left in the granulopoiesis had disappeared, there were abundant quantities of mature granulocytes. There were still many megacaryocytes, but whereas before the operation only 15 per cent had been plate-

Table 2.  
*Bone Marrow Differential Counts.*

	Nov. 11th, 1944	Febr. 16th, 1945
Hemocytoblasts .....	1 %	1.5 %
Promyelocytes .....	6	1.5
Neutr. myelocytes .....	28	16
Eos. — .....	1	2.5
Metamyelocytes .....	27	7
Staff cells .....	16	15
Segmented neutrophils .....	1	34
— eosinophils .....	1	4
— basophils .....		0.5
Lymphocytes .....	2	3
Monocytes .....	0.5	1
Plasma cells .....	1.5	1
Reticulum cells .....	1	
Erythroblasts I .....		1
Erythroblasts II .....	1.5	1
Normoblasts .....	12.5	12

let-producing, there were now 80 per cent which produced an abundance of platelets.

The patient has been followed-up for a little over two years after the operation and has during that time been subjectively completely well, and there has been no epistaxis or even the slightest symptoms from the mouth or fauces. On the other hand, the operation has not had quite the desired effect on the hematologic state, inasmuch as there is still some neutropenia; and though the last control examination, a little over two years after the operation, showed 300,000 thrombocytes, one examination, on June 19, 1946, also here showed a somewhat diminished count (80,000). In periods both before and after the operation, the eosinophile leucocytes have shown high values both absolute and relative; it seems as if the inhibition has not involved these cells. The monocyte values, which all the time had been high, rose markedly after the operation, but the appearance of the cells was always normal, there were no immature monocytes. At no time were there any immature granulocytes in the blood, or any nucleated red cells. On the other hand, there was a slight increase of reticulocytes in the first days after the operation.

There can hardly be any doubt that in this case the spleen was chiefly determining for the patient's thrombo- and granulocytopenia. Increase of the reticulum cells in that organ is a feature common for most cases of splenogenic inhibition in

the marrow. That sometimes complete normalisation of the hematologic state is not obtained is usually explained as due to the circumstance that in such cases the affection is generalised to the whole reticuloendothelial system. This was possibly also so in the case reported here.

The patient was number six of a sibship of twelve. As it may perhaps be more than a simple coincidence that a brother two years younger two years afterwards was admitted to the Radium Center suffering from subacute blast leukosis, I here briefly give the record of his case also:

The patient, a gardener, 25 years old, unmarried, was admitted to the Radium Center for Jutland Dec. 27, 1946 (Record. no. 4081/46). His health had on the whole been good until his present illness had begun, six weeks before admission, with pain first in the left and shortly after in the right knee, and then in the left shoulder. The joints were tender, perhaps a little swollen. At the same time, he had been feeling tired and had had several attacks of nosebleed. At admission he was rather fatigued and anemic, but not emaciated. The spleen was slightly enlarged, but there were no swollen lymph nodes, neither was there any enlargement of the liver. The knee and shoulder joints were tender to touch, but there was no redness or swelling. Blood examinations showed: sedimentation rate 21 mm. h., erythrocytes 2,920,000 per cmm., leukocytes 17,000, platelets 125,000. Differential count: blasts 9 %, myelocytes 2 %, segmented neutrophils 13 % eosinophils 1 %, lymphocytes 20 % normoblasts 1 % of nucleated cells. The sternal marrow was almost pure blast marrow. Roentgenographs showed leukemic bone changes (rarefaction, periosteal elevation) in the shafts of right femur and both humeri.

The diagnosis is not difficult, it was a case of blastic leukosis. That it occurred in a brother of the first patient may, of course, have been a mere coincidence; on the other hand there are cases reported in the literature in which a familial constitutional disposition seems to express itself by different disorders of the hemopoiesis, so that, for instance, blastic leukosis may occur in a family where other members suffer from anemia, granulocytopenia or the like (see: Bichel, 1940). In this case, the other brothers and sisters could unfortunately not be examined, but according to statements none of them present any signs of disease.

### Summary.

The author reports a case of chronic neutro-thrombopenia in a man, 25 years old, who since childhood had been more or less of an invalid from recurrent stomato-gingivitis, attacks of febrile angina and frequent, profuse nosebleeds. Examination of the bone marrow showed signs of maturation arrest of the granulo-thrombopoiesis. Splenectomy was performed. The spleen was slightly enlarged and histologically showed minor changes, especially some proliferation of the reticulum cells and slight perivascular fibrosis. After the splenectomy, the granulocyte and thrombocyte counts promptly rose, the patient was symptomatically cured and has since for more than two years been entirely fit for work, though continued blood examinations still show some granulocytopenia. A younger brother was shortly afterwards admitted, suffering from sub-acute blast leukosis. His case is briefly described. The author briefly discusses the splenic inhibition syndromes and the importance of familiarity with them and with the value of splenectomy in such cases.

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# FOLIC ACID IN THE TREATMENT OF PERNICIOUS TAPEWORM ANEMIA<sup>1)</sup>

*Diphyllobothrium latum and Pernicious Anemia. XI.<sup>2)</sup>*

By

*Bertel von Bonsdorff, M. D.*

*Helsingfors, Finland.*

## *The Problem.*

It is now a clinically well-established fact that folic acid (pteroylglutamic acid) is a highly effective therapeutic agent in cases of cryptogenetic pernicious anemia, of other types of macrocytic anemia and of sprue. A review of the relevant literature has recently been published by Cartwright.

Folic acid has not yet been tested in cases of pernicious anemia due to infestation with *Diphyllobothrium latum* and the object of this paper is to demonstrate the value of the preparation in this form of anemia.

## *Method and Results.*

Folic acid was tested in 4 cases of pernicious anemia in tapeworm carriers. In 3 of them (Cases 86, 87 and 88) it can be regarded as certain that the anemia was due to the worm infestation because the patients were only 19, 28 and 19 years old respectively, and because they had, at least on some occasion, free hydrochloric acid in their gastric contents while the anemia was manifest. The fourth patient (Case 89) was 53 years old and exhibited achlorhydria, so it cannot be completely excluded that here was a coincidence of anemia and tapeworm infestation. Yet this seems improbable, considering that she had not previously suffered from anemia and that her recovery was

<sup>1)</sup> Aided by a grant from the Ella and Georg Ehrnrooth foundation.

<sup>2)</sup> Latest communication (X): Acta med. scand. 129, 213 (1947).

apparently complete when the anemia was cured and the worm expelled. All the patients showed the typical blood picture of a pernicious anemia. The sternal punctate, examined in Cases 86, 87 and 89, was also typical of this disease. No patient had any complicating illness. The bowel functioned normally in each case.

Synthetic folic acid was used for the test and was administered per os in tablets of 5 mg. Some of these had been kindly placed at my disposal by Prof. E. Meulengracht, Cöpenhagen, and Prof. J. Waldenström, Upsala.

The tests were planned as follows: after some days observa-

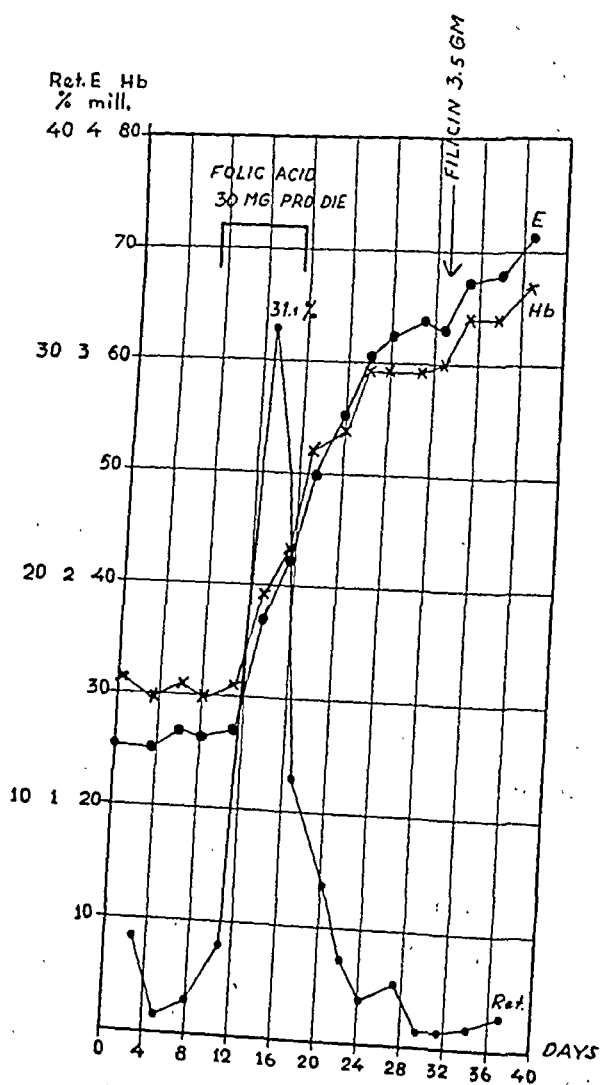


Fig. 1. Case 86.

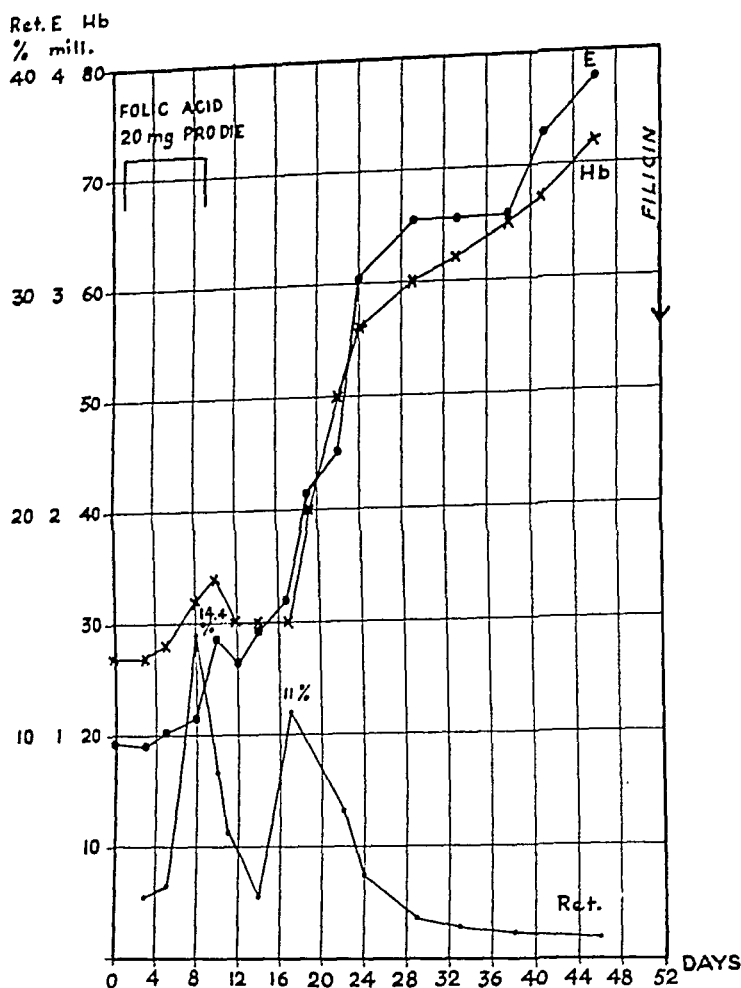


Fig. 3. Case 88.

creased on an average 100,000 per day and the hemoglobin value rose from 30 to 60 per cent. At the same time the thrombocytes increased with certain fluctuations from 56,000 to something under 200,000 and the leukocytes from 1,600 to 3,700 (on discharge 7,500). The sedimentation reaction which 3 days after the treatment with folic acid began, was 90 mm/1 hour was 25 mm/1 hour 2 days after the medicine was postponed, and at the time of the worm cure was only 10 mm/1 hour. Already a few days after the treatment began the patient felt a subjective improvement. At the worm cure 45 m of *Diphyllobothrium latum* were expelled and after that the blood improvement continued, but there was no new reticulocyte crisis. The

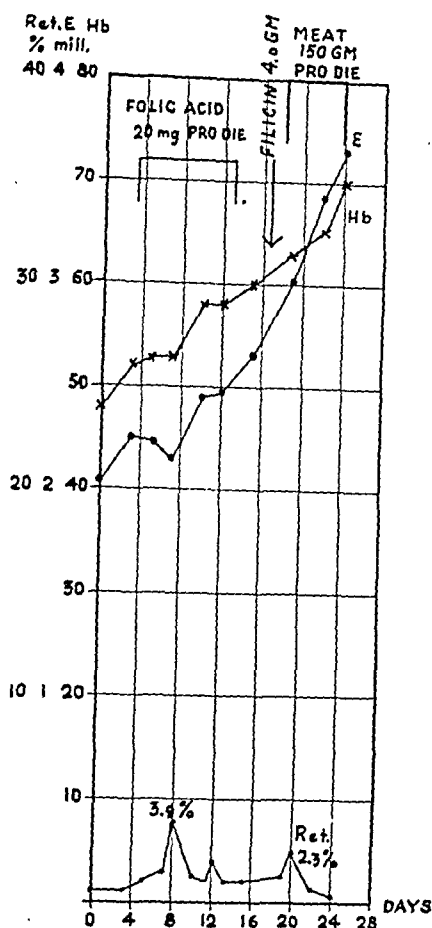


Fig. 4. Case 89.

anti-anemic effect of the folic-acid treatment had obviously been maximal.

Case 87 (Fig. 2) ran a similar course in all respects. This patient was given 30 mg "Folacid", Union Chimique Belge, per os for 7 days.

In Case 88 (Fig. 3) during the treatment with 20 mg Folvite and Folacid for a period of 9 days a reticulocyte response arose with two peaks and a very long lasting blood remission. The blood values returned almost to normal before the worm was expelled. At the same time the sedimentation reaction fell from 128 mm/1 hour to 27 mm/1 hour. When admitted the patient had anemia fever which disappeared 5—6 days after the

treatment was begun. In all probability the powerful remission was due solely to the folic acid treatment. It is less probable that a spontaneous remission would have coincided with its effect.

In Case 89 (Fig. 4) the initial values for hemoglobin and erythrocytes were somewhat higher than in the previous cases. The reticulocyte crisis was also relatively insignificant. Yet a remarkable improvement of the red blood picture and the condition otherwise was noticed. Preparation used: Folvite, 20 mg for 10 days.

### *Comments.*

It has previously been shown that a pernicious anemia due to *Diphyllobothrium latum* responds to treatment with liver preparations per os or parentally and to stomach preparations per os just as satisfactorily as the cryptogenic and other forms of pernicious anemia. On the other hand, mixtures of gastric juice and meat or other sources of extrinsic factor are ineffective in tapeworm anemia, in contrast to what is true of the cryptogenetic form.

The results here reported show convincingly that folic acid administered per os in doses of 20—30 mg per day produces a quick and powerful reaction in cases of pernicious tapeworm anemia. This result agrees with what has been proved in other forms of macrocytic and megaloblastic anemia.

Thus the anti-anemic effect of folic acid is not impaired by the presence of *Diphyllobothrium latum* in the intestinal canal. To prove this was the main object of these investigations. It was, therefore, not considered necessary to examine the effect of the drug on the parenteral route. In all probability a good effect would also have been achieved in this way.

The result is of interest because each new gain in research concerning the pernicious anemia should be tested as to the extent to which it can also be applied to the pernicious tapeworm anemia.

According to a modern theory put forward by Welch, Heinle, Nelson and Nelson pteroylglutamic acid is released from pteroylheptaglutamic acid (Vitamin B<sub>12</sub>-conjugate) through the action of Vitamin B<sub>12</sub>-conjugase in normal individuals but not

in patients with cryptogenetic pernicious anemia. This seems to indicate that in the latter disease it is the conjugase system which is at fault, and should account, in part at least, for the failure of the patients to derive adequate amounts of folic acid from the diet since in nature the compound may occur principally in the conjugated form.

My results are not inconsistent with the possibility that this theory is correct. I have shown that patients with pernicious tapeworm anemia secrete intrinsic factor, but that *Diphyllobothrium latum* in vivo checks the reaction between the intrinsic and extrinsic factors. The final anti-anemic product, the liver factor, on the other hand, is not impaired by the worm, nor as shown above is the folic acid. On the other hand it may be thought that the worm by its presence checks the conjugase activity and in this way in certain cases can give rise to pernicious anemia. It should be stressed that it has not been possible to prove the identity either of intrinsic factor and conjugase, extrinsic factor and Vitamine B<sub>12</sub> conjugate, or liver factor and folic acid. Continued investigation is necessary for the solution of that problem.

### *Summary.*

Folic acid (pteroylglutamic acid) administered in doses of 20–30 mg per os daily for 7–10 days produced a very good remission in cases of pernicious anemia due to infestation with *Diphyllobothrium latum*. It thus appears that folic acid is no more destroyed by the presence of the tapeworm in the intestinal canal than is the anti-anemic liver factor.

### *Cases.*

*Case 86.* IV. Medical Clinic, Maria Hospital, Helsingfors, 1355/47. Woman of 19 years. Fig. 1. Healthy in childhood. Worm segments noticed in the stools at the age of 15. Has never had a worm cure. Has been tired for some months, sometimes had diarrhoea. During recent months has felt nauseated and been giddy.

Pale, slightly icteric. Ankle jerks absent. Tongue smooth. No fever. Strong urobilin reaction in the urine. The gastric contents (20 ml) aspirated in the morning (on admission) contained free hydrochloric acid (free HCl 27, TA 49). After insulin stimulation only 5 ml mucus of acid reaction were obtained, no free HCl.

Worm cure: 45 m *Diphyllobothrium latum* expelled.

Table I. Blood picture and other hematological data  
on admission.

Case	Age	Sex	Hb Sahli	RBC	Colour Index	Platelets	WBC	Differential count (per cent)							Nucleated RBC /100 WBC	Icterus index	Diameter of RBC ( $\mu$ )	
								Basophils	Eosinophils	Myelocytes and N. juvenils	N., rod shaped	N., segmented	Lympho- cytes	Monocytes			Mean diameter	Limits
86	19	f.	31	1.280.000	1,19	56.000	1600	0,5	2,0	4,0	2,0	45,0	46,5	—	—	1:14	7,67	5—10
87	28	f.	37	1.520.000	1,23		6700	0,5	1,0	4,5	3,0	35,5	51,0	4,5	2	1:7	7,85	3—12
88	19	f.	27	980.000	1,35		4000	—	3,5	1,0	2,0	22,5	70,0	1,0	—	1:7		
89	53	f.	48	2.040.000	1,20		4400	—	6,0	—	2,0	56,5	28,5	7,0	—	1:7	7,50	4,5—10

*Case 87.* IV. Med. Clin. 856/47. Woman of 28 years. Fig. 2. Previously healthy. For some months has felt tired, had soreness of tongue and a bad appetite. Has seen worm in the stools.

Pale, slightly icteric. Tongue smooth, reddish. No fever. Ewald-Boas (on admission): 6 ml, free HCl 10, TA 30.

*Case 88.* St. Michel General Hospital. 1608/47. Woman of 19 years. Fig. 3. Has been tired for some months. Headache the last week. Pale. Temperature the first 10 days ad 38—39° C. Hands and feet slightly swollen. Ewald-Boas (on admission): 4 ml, free HCl 10, TA 45.

This case was kindly placed at my disposal by Dr. V. Dahlström, head of the medical department, for the testing of folic acid.

*Case 89.* I. Medical Clinic, Helsingfors. 159/47. Woman of 53 years. Consulted me on account of epigastric pain and dyspnoea for some months. Had lost 2—3 kg in weight. Frequent diarrhoea. Giddiness, nausea, headache and sleeplessness for a time. Had once had a worm cure when young. Had seen worm in the stools several times during the last year. The patient was admitted to I. Medical Clinic, whose chief, Prof. W. Kerppola kindly allowed me to test folic acid treatment on her.

Subicteric. Tongue smooth. No signs of cardiac disease. No fever. Ewald-Boas (on admission): 40 ml, free HCl 0, TA 7.

Worm cure: 19,5 m *Diphylobothrium latum* expelled.

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*From the Copenhagen County Hospital, Gentofte, Denmark. Pathological Department (Chief Pathologist: Søbørg Ohlsen) and Medical Department C (Chief Physician: Siggaard Andersen) and from the Zoophysiological Department of the Agricultural Experimental Laboratory (Chief: Professor H. Møllgaard), Copenhagen, Denmark.*

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## ON THE EFFECT OF TOTAL RESECTION OF THE FUNDUS VENTRICULI IN THRIVING SWINE UPON THE ANTI-ANEMIC FACTOR CONTENT OF THE LIVER

By

*P. Borch-Madsen and A. Søbørg Ohlsen, M. D.*

The therapeutic experiments performed by Meulengracht in 1934 in order to locate the "intrinsic factor" in the mucosa of the stomach gave a really surprising result. These experiments were carried out with dried, defatted, powderized tissues from the well-defined cardia, fundus and pyloric portion of swine stomach. The fundus powder was found to be inactive in the treatment of patients suffering from pernicious anemia, while the pyloric powder gave remission of the disease with the same intensity as obtained with liver preparations. The cardiac powder had a slight remittent effect.

The gastric achylia, which is a characteristic feature in pernicious anemia is due to severe chronic inflammatory changes in the fundic mucosa accompanied by atrophy of the specific glandular cells: chief cells and parietal cells. They are replaced by uncharacteristic columnar epithelial cells, approximately of the neck-chief cell type, or with goblet cells. In contrast hereto, the mucous membrane of the pyloric portion is almost intact histologically.

In view of this fact it would seem reasonable to expect the fundic powder to be the most active in the therapeutic effect. But this was not the case when material from swine stomach was given to the patients. In 1946, however, Landboe-Christensen & Plum showed powderized fundus humanus to be thera-

apeutically effective against pernicious anemia, demonstrating thus that in this respect there is a difference in the stomach of man and swine. No explanation of this difference is found in the histological features, which appear to be identical in the two species. Possibly a more thorough investigation of the enzyme systems in these two mucosal types may lead on to a satisfactory explanation. But, so far, the investigations aimed in this direction have not revealed anything to settle this properly. Thus, at present, it simply has to be taken as established that therapeutically the powder from swine fundus is negative, that from the fundus humanus positive. Elucidation of this feature in other mammalian species seems desirable. At any rate, the experiments reported by Landboe-Christensen & Plum have brought harmony in the conception of the central position of the fundus of the stomach in the clinical picture of pernicious anemia.

Petri and collaborators have reported a number of experiments with total resection of the fundus on swine, giving rise to a morbid condition interpreted as pellagra. The pigs treated in this way were losing in weight, becoming cachectic, simply anemic, with pronounced skin changes and pareses. From the liver of such pigs a preparation was made in the same way as "hepsol" (therapeutic liver preparation against pernicious anemia), but this was found to be ineffective in untreated cases of pernicious anemia. This, we think, is connected with the character of the illness from which the pigs were suffering. That this illness was not directly associated with the fundic gastrectomy is evident from the experiments reported by Borch-Madsen who succeeded in keeping the fundectomized pigs thriving on an adequate diet. The experimental results obtained by Petri and collaborators with fundectomized pigs, we think, may be taken to suggest that in patients with pernicious anemia the mechanism involved in the exchange of the antianemic principle is highly sensitive. In patients of this character the appearance of infectious lesions brings about that the otherwise sufficient dosage of antianemic principle has to be multiplied many times in order to produce remission of the disease. Whether we here meet with an impairment of the capacity of the bone marrow for utilization of the antianemic principle, or whether the pre-

paration of this principle in the liver has been disturbed so that its utilization has become defective, is still an unsettled question. If in Petri and collaborators' experiments the diet of the pigs has been adequate quantitatively and qualitatively, some disease of unknown nature has led to cachexia of the animals and prevented the building-up of the antipernicious principle in the liver.

In support of this view we shall report a couple of therapeutic experiments on previously untreated patients suffering from pernicious anemia who were given "hepsol" made from the liver of totally fundectomized pigs that were thriving over 175 days after the operation. In these animals the fundic resection had induced a simple achylic anemia of the Faber type, whereas no evidence of pernicious anemia was observed in the experimental series. These swine presented no evidence of any nervous affection and no skin changes.

In the therapeutic experiments, hepsol made from the liver of these animals was found to induce a rise in the reticulocyte count in hitherto untreated patients suffering from pernicious anemia. This is in harmony with the negative results obtained by Meulengracht on administration of powderized swine fundus to such patients.

As to the technique employed for the production of achylia through fundectomy of the stomach, besides details in the feeding and living conditions of the achylic pigs, the reader is referred to the dissertation of Borch-Madsen, as the present liver material originates from the achylic swine included in that work.

*Experiment 1* (Dep. C, Copenhagen County Hosp., Record. No. 1450/44).

The patient was a woman, aged 67, admitted 1/9—2/11/44 under the diagnosis: Pernicious anemia.

Through many years the patient had been suffering from a heart lesion, for which she was granted invalidity insurance benefit in 1932. In addition, she was suffering from obesity and chronic bronchitis; and she gave a past history of syphilis. Now she was admitted on account of an overwhelming tiredness.

Weight: 72,5 kg. Height: 152 cm. Blood pressure: 170/85. Wassermann: Negative. Urine: No albumin or sugar. Ewald test meal: 30+53 cc.; poorly chymified; free acid 0; total acidity 20.

Hemoglobin: 50 %. Red blood count: 1,860,000. Color index: 1.25.  
White blood count: 1580.

Sternal punctate: Per 400 cells of the "white system", the following cells of the "red system" were found:

Proerythroblasts .....	6
Erythroblasts, basophil .....	7
— eosinophil .....	14
Promegaloblasts (1 in mitosis) .....	97
Megaloblasts, basophil .....	34
— eosinophil .....	24

The erythrocytes showed very pronounced anisocytosis and megalocytosis. In addition a few polychromatic erythrocytes were seen.

This blood picture is characteristic of megalocytic anemia of pernicious type.

As to the treatment, see Fig. 1.

The patient stated of her own accord that mentally she felt much better after the first injections of the hepsol employed, being not by far so tired and unreasonable as before.

The treatment with our hepsol was followed by a smaller rise in reticulocytes — much smaller than was justified to expect from the red blood count. Subsequent treatment with "hepsol fortior" gave a secondary rise in reticulocytes of the magnitude expected, and followed by a rise in the red blood count and hemoglobin percentage.

*Experiment 2* (Dep. C, Copenhagen County Hosp., Record No. 1668/44).

Male, aged 73, admitted 28/10—16/12/44.

Diagnosis: Pernicious anemia; sequelae of colostomy for cancer of the rectum; myocardiac degeneration.

In 1938, cancer of the rectum was diagnosed and treated with 1) colostomy, 2) abdominoperineal extirpation of the rectum.

Microscopy: Adenocarcinoma.

On present admission, the colostomy was functioning well, and there was no sign of recurrence of the adenocarcinoma.

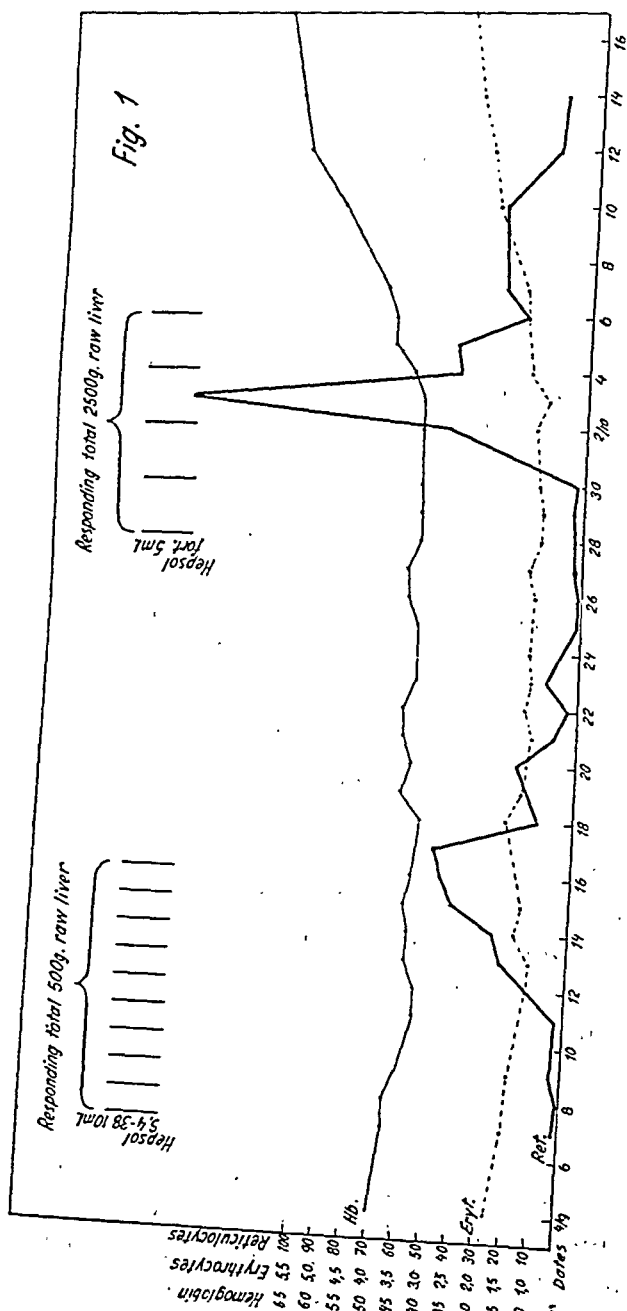
Through the last months the patient had been complaining of increasing tiredness, on which account he now was admitted.

Weight: 70 kg. Height: 177 cm.

Ewald test meal: 10+0 cc.; poorly chymified; free acid 0, total acidity 10.

Hemoglobin: 43 %. Red blood count: 1,490,000. Color index: 1.38.

Sternal punctate: Per 400 cells of the "white system", the following cells of the "red system" were found:



Proerythroblasts .....	3
Erythroblasts, basophil .....	3
— eosinophil .....	3
Promegaloblasts (2 in mitosis) .....	36
Megaloblasts, basophil .....	39
— eosinophil .....	32

The erythrocytes showed a considerable degree of anisocytosis with megalocytosis and some polychromatophilia. Thus the bone marrow showed the presence of a megalocytic anemia of pernicious type. The megalocytic regeneration type was accompanied by the presence of many large neutrophil, somewhat polymorphonuclear myelocytes.

As to the treatment, see Fig. 2.

Mentally the patient was feeling much better shortly after the institution of the treatment.

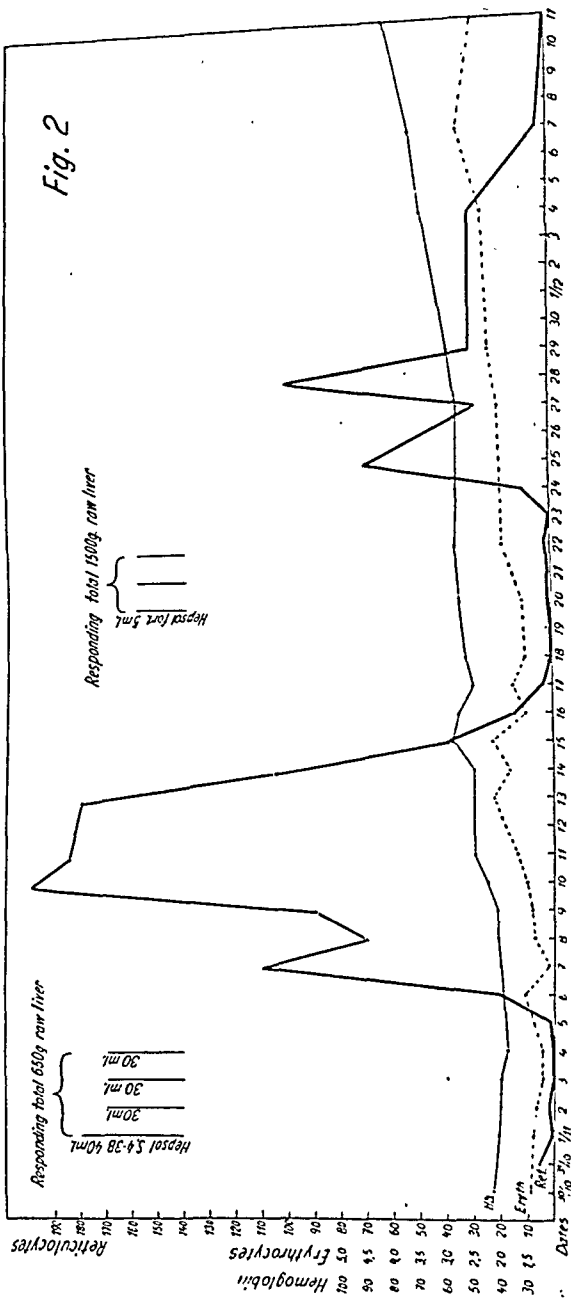
The amount of hepsol that could be prepared from our liver material was only slight. The pharmaceutical manufacturing firm, Medicinalco Ltd., Copenhagen, was so accomodating as to prepare the "hepsol" for us, and Dr. Munk Plum has calculated the reticulocyte-maturing factor of this hepsol and found it a little lower than normally. Undoubtedly the first dosage has been too diffuse and weak, on which account it was altered in Exp. 2 so as to make a comparison with hepsol practicable.

In Exp. 2 we meet with a convincing rise in the reticulocyte count. Still, after a pause of 16 days, treatment with hepsol fortior was given, and this brought a secondary rise in the reticulocyte count to about one-half of the first value.

This has to be looked upon as resulting from insufficient administration of our hepsol, not as a disqualification of this hepsol.

### *Summary.*

Two patients suffering from pernicious anemia are treated with "hepsol", prepared from swine on which previously total fundectomy of the stomach had been performed. In the first patient a diffuse and weak dosage of the "hepsol" resulted in a moderate rise in the reticulocyte count. In the second patient a more concentrated dosage of our hepsol was followed by a sufficient rise in the reticulocyte count. But lack of "hepsol"



material precluded any continuous treatment with this substance.

The conclusion is drawn that the fundic portion of the *swine stomach* is of no significance to the formation of the antipernicious principle in the liver.

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## ACUTE HEMOLYTIC ANEMIA (TYPE LEDERER)

By  
*Holger Buch, M. D.*

Hitherto 5 cases of acute hemolytic anemia of the Lederer type have been reported in this country (Tage Christiansen, Knud Hoyer, Roelsen and Soeborg Ohlsen). Of these cases, only one occurred in a child, 3 years old (Hoyer), while the remaining 4 patients were adults.

In the Medical Department E of the Frederiksberg Hospital we have had occasion to treat a boy, 9 years old, who was admitted with symptoms of this disease. In this boy the development and course of the lesion were characteristic of the acute form of the disease, and hence it will be appropriate to give a brief abstract of the case history, with mention of the more important laboratory examinations performed.

### *Case Record.*

(No. 72/45). Boy, 9 years old. Admitted 7/12/44. Discharged 6/1/45.

Family history negative as to tendency to diseases of the blood or similar conditions.

The patient is an only child. His past history is negative except for an attack of rubella and tendency to angina.

*Present illness:* Onset 3 days before admission with a little headache, which persisted. On the following day the boy became dizzy and had attacks of vomiting, with a rise in temperature to 38°. On the next day (the day before admission) the skin of both hands was noticed to have become marmorated. He was brought to the hospital on account of increasing lassitude. No treatment had been given at home, no drugs, in particular no form of sulfanilamide.

On the admission, the patient was markedly exhausted and extremely anemic. He was lying restless, with facial twitchings, apparently hazy, though able to give a few adequate answers.

On the skin, especially on the extremities, small ulcers were

scattered about, resembling mostly scratching of prurigo elements. There were no petechiæ, but on the extremities the skin showed a pronounced, wide-meshed bluish marmoration.

There was slight rigidity of the neck and the back. Otherwise the physical examination showed no abnormality. In particular, there was no enlargement of peripheral lymph glands; nor any enlargement of the liver and spleen.

Hemoglobin: 28 %. Red blood count: 900,000. Color index: 1.4. The red blood picture showed mostly normocytes, but there was pronounced macrocytosis and microcytosis, together with several normoblasts and a few chromophilic cells. White blood count: 51,500. Differential count: neutrophil staff-nuclears: 11 %; segment-nuclears: 38 %; large lymphocytes: 10 %; small lymphocytes: 30 %; monocytes: 6 %; transitional forms: 5 %. Blood grouping: Type 0.

Spinal fluid: Cells 3/3; albumin 10; globulin 0.

On the day after admission a blood transfusion was given, 300 cc., after which the boy straightened up somewhat and became more quiescent.

As there was no change in his anemic, wax-pale appearance, blood transfusion was given also on the following 2 days, during which he became clear, improved markedly and began to eat.

As the hemoglobin percentage increased but slowly, the employment of blood transfusion was continued, altogether 6 transfusions being given in the first 13 days after admission.

Temperature: 39° on the day after admission but otherwise varying during the first week between 37.2/37.4 and 37.8/38.4, whereafter it became normal.

At no time was there any palpable enlargement of the spleen or liver.

The boy kept feeling well, and he was discharged one month after admission.

*Reexamination*, 1 year later. During this year the boy had been feeling perfectly well, having not had any illness whatever, nor any rise in temperature. He was always in good form, and active, never tired. The appetite was good, and he had been gaining gradually in weight. He looked healthy. There was no enlargement of peripheral lymph glands; the liver and spleen were not palpable; and there was no icterus.

#### *Other Laboratory Examinations:*

Urine: No albumin, blood, pus or sugar. 10/12. +urobilin, 1/30; 11/12 and 12/12: +urobilin 1/10.

Icterus index, 11/12: 10.

Hemoglobin and reticulocyte values, see Fig. 1.

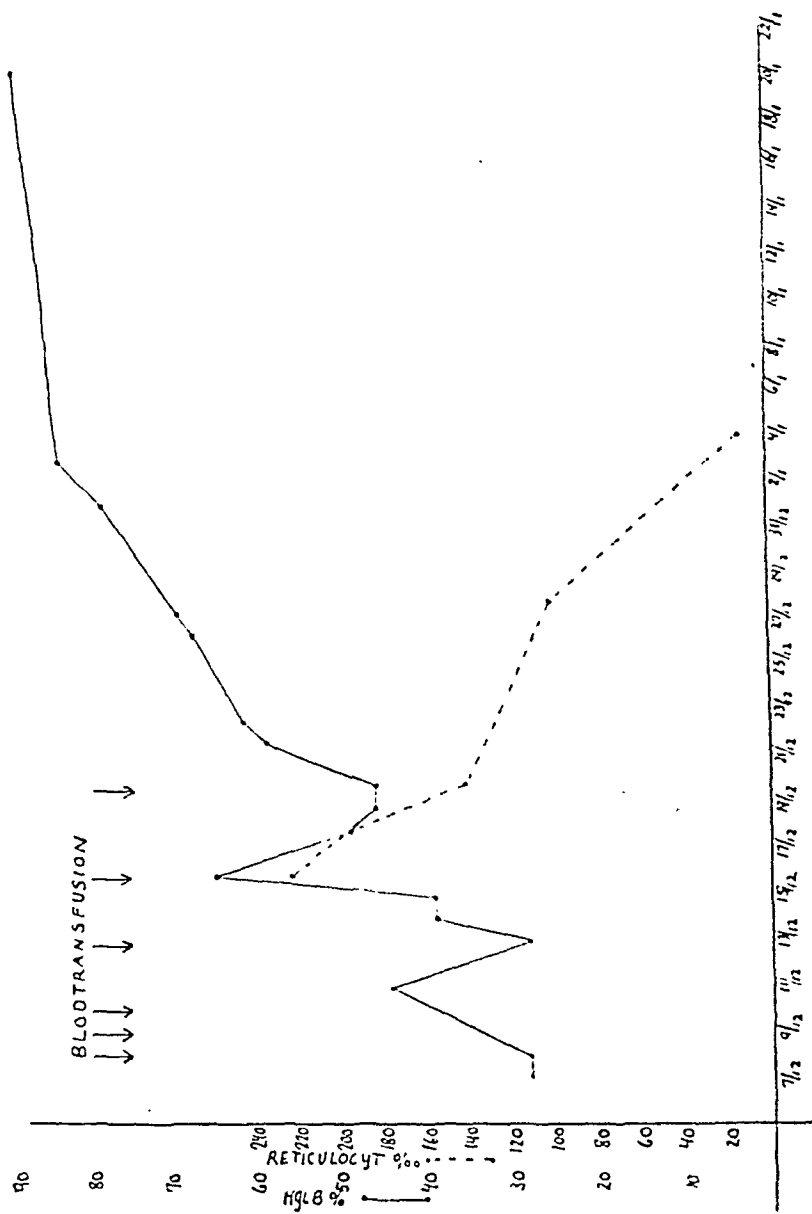


Fig. 1.

*Sternal punctate, 11/12:*

Myeloblasts .....	6.50 %
Promyelocytes .....	2.75 %
Neutrophil myelocytes .....	13.50 %
Eosinophil — .....	3.25 %
Basophil — .....	0
Metamyelocytes + neutrophil staff-nuclears ..	35.50 %
Neutrophil polymorphonuclears .....	18.00 %
Eosinophil leukocytes .....	0.75 %
Basophil — .....	0
Lymphoblasts .....	0.25 %
Lymphocytes .....	18.50 %
Monocytes .....	0
Plasma cells .....	0.50 %
Megakaryocytes .....	0
Reticulum cells .....	0.50 %

Per 400 cells of the "white system" the following counts were found for the "red system":

Erythrogonia .....	31 (normal 4—6)
Erythroblasts, basophil (12 in mitosis) ..	238 ( — 20—30)
— eosinophil .....	270 ( — 30 )
Shadows .....	12

The erythrocytes show marked anisocytosis with macrocytosis and pronounced polychromasia. Corresponding hereto, there is a very active erythropoiesis. Some of the erythrogonia are rather large.

The total picture corresponds to a rather severe toxic infectious effect on the marrow. There are signs of a rather severe anemia of simple type, also a shift to the left in the "white picture". No evidence of leukemia is seen, nor any tumor cells.

(signed A. Sjøborg Ohlsen).

Red blood picture, 9/12 and 11/12: Similar findings as on admission.

White blood counts: On 9/12: 44,300; on 11/12: 20,140; on 25/1/45: 8500.

Repeated differential counts showed similar values as on admission.

Thrombocytes: 9/12: 130,000; on 13/12: 176,000.

Sedimentation rate, 12/12: 160 mm/1 hour.

Wassermann: Negative.

Clotting time, 9/12: 1½ min. Bleeding time, 11/12: 1 min. Capillary resistance, 11/12: 2 petechiae. — Osmotic resistance, 20/12: Beginning hemolysis, 0.46 %; total, 0.40 %.

Feces: Benzidin test negative; no pathogenic intestinal bacteria.

Blood cultures, 8/12 and 11/12: negative, in particular with regard to growth of leptospira.

Widal test, 14/12 and 20/12: Positive reaction with typhoid O antigen in dilution 1:50. Weil test, 14/12: negative.

Tuberculin test (Moro): Negative.

Reexamination, 8/12/45: Hemoglobin: 95 %. Red blood count: 4.3 millions. Color index: 1.05. White blood count: 7600 (neutrophils: 65 %; eosinophils: 2 %; lymphocytes: 31 %; monocytes: 2 %).

*Epicrisis:* A boy, 9 years old, with a past history of good health, becomes suddenly ill (from no known cause), exhausted, showing within a few days a fall in hemoglobin to 28 %, accompanied by microcytosis and macrocytosis, together with the appearance of normoblasts in the peripheral blood, leukocytosis, reticulocytosis and urobilinuria. He improves after blood transfusion. Still, it is necessary to give him a total of 6 transfusions in the course of 13 days. — After this he becomes perfectly well. On reexamination one year later, he has been perfectly well since his discharge, and now the blood examination shows only normal features.

### Discussion.

In the first days after the admission of the patient we were rather uncertain as to the diagnosis of his illness.

In view of his age and his appearance on admission we were most inclined to think that here we might be dealing with an instance of *acute leukemia*. But the blood examinations and the subsequent course of the lesion excluded this possibility. — Likewise, *hemorrhagic anemia* could be excluded, as the history of the patient was perfectly negative with regard to any preceding hemorrhage; and, furthermore, no evidence of occult bleeding could be found.

Then it might seem conceivable that the lesion consisted in some *toxic damage to the bone marrow* — brought about either by an infection or by poisoning with one of the substances known to have a toxic effect on the bone marrow or blood cells. But the negative result of the repeated blood cultures as well as the entire course of the case excludes the possibility of a septicemia. Besides, the child has not been given any drugs immediately before the onset of the illness nor before his admission to the hospital, and thus a toxic damage seems unreasonable.

As the family history is negative with regard to the occurrence of *familial hemolytic jaundice*, also this possibility is out of the question. On the other hand, it is more difficult to exclude the possibility of an *acquired hemolytic jaundice*. Still, the macrocytosis, the normal osmotic resistance and the course of the case goes strongly against this possibility.

Nor does the course of the illness in our patient resemble *paroxysmal nocturnal hemoglobinuria* or *cold hemoglobinuria*. Thus no hemoglobinuria was demonstrated on his admission; the Wassermann test was negative; and there has been no recurrence of his illness since. Unfortunately, no examination was made for cold hemolysin.

So it looks as if this must have been a case of the *acute hemolytic anemia* described by Lederer in 1925 and 1930.

This type of hemolytic anemia is characterized by its acute onset and short duration, going on to complete recovery — spontaneous or following blood transfusion — or terminating fatally after a few days. Dyke & Young have described a few cases of a more chronic character, it is true, but they appear to constitute a special group.

Recurrence of the disease appears not to have been reported in any instance.

After a few days' fever, malaise and influenza-like symptoms with dedolations and, sometimes, gastro-intestinal symptoms (especially in children), a very pronounced anemia develops, accompanied by a more or less intense icterus together with urobilinuria; sometimes also marked hemoglobinuria. Besides the anemia, as a rule the blood examination shows also microcytosis as well as macrocytosis, leukocytosis and rather numerous normoblasts and chromophilic cells. Furthermore, there gradually appears a pronounced reticulocytosis as sign of the intensive blood regeneration.

An interesting phenomenon is the auto-agglutination of the patient's erythrocytes demonstrated by Greenwald, Gjordanò & Blum that disappears after blood transfusion. On the whole, the effect of blood transfusion is very striking. Often it takes only a single transfusion to obtain complete recovery.

As to the *etiology* of the disease, it is still obscure. Roelsen and Soeborg Ohlsen think that the anemia is due to the effect

of a hemolysin, either owing to a direct toxic-infectious agent or to a congenital or acquired latent disposition that becomes activated by toxic-infectious processes or, perhaps, by some psychic trauma.

According to a private communication from Dr. E. Somekh, Bagdad, the disease is said to be very frequent in Iraq, where its occurrence is said to be markedly seasonal, as it appears almost exclusively when a particular sort of green peas is blooming. The disease is taken to be of allergic nature and it has been possible to produce a vaccine that protects against this disease completely. The course and treatment of the disease are quite the same as described everywhere. If blood transfusion is given early enough, practically every patient will recover. Several hundred cases of this kind are said to occur every year in Bagdad alone.

Besides, the eliciting factor just mentioned, no doubt, there must be other factors too. In our case it was not possible to find any factor that conceivably might have elicited such an allergic reaction. In addition, it is to be pointed out that in our case the disease commenced in the beginning of December. The positive agglutination test with typhoid O antigen demonstrated in our case may hardly be assigned any particular significance. During his illness, our patient had no gastrointestinal disturbances whatever, and the examination of the feces revealed no pathogenic intestinal bacteria. Our patient has never had any symptoms of some typhoid infection, and he has never been vaccinated against typhoid fever.

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## HYPERSPLENISM: SOME PRELIMINARY OBSERVATIONS

By

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It has long been known that enlargement of the spleen is often associated with a reduction in the number of red cells, white cells, or platelets in the circulating blood. Some observers have believed that there is a causal relationship between the splenomegaly and the accompanying anemia, leukopenia, or thrombocytopenia. This concept has shown a gradual evolution over the years.

Apparently Gretzel in 1866, in a description of "splenic anemia," (1) was the first to suggest that the spleen might be responsible for a reduction in the circulating blood cells. Banti (1893—1910), (2) popularized the designation of "splenic anemia," and following his observations, almost any anemia associated with splenomegaly and in which no other etiologic agent could be found was called "Banti's disease," on the assumption that the spleen was the responsible agent. Banti, as well as Osler (3), noted the frequent occurrence of leukopenia in cases of "splenic anemia." Cabot (4) who was skeptical of a causal relationship between the spleen and the anemia, pointed out that the leukopenia was often more striking than the anemia. Frank in 1916 suggested that the leukopenia might be due to the enlarged spleen, and used the term "aleukia splenica" for the condition, (5). About the same time a causal relationship between the spleen and thrombocytopenia (idiopathic thrombocytopenic purpura) was suggested by Kaznelson (6). Thus, by 1916 three cytopenias had been described in association with a possible dysfunction of the spleen: anemia, leukopenia, and

thrombocytopenia. In the first two, splenomegaly was common; in the last rare.

The manner in which a large spleen might produce reductions in blood cells (cytopenias) has been widely discussed. In "hemolytic splenomegaly", (hemolytic anemia) as studied intensively, by Banti (7) and Micheli (8), splenectomy was often found to be curative. It was known that the spleen destroyed excessive numbers of red cells; i.e. this splenic cytopenia was evidently due to an excessive destruction of the red cells by the pathologic spleen. By analogy, Kaznelson attributed the thrombocytopenia of idiopathic thrombocytopenic purpura to an excessive destruction of the circulating platelets by an abnormal spleen; and many observers have blandly accepted this mechanism to date. The leukopenia of certain cases of splenomegaly has also been explained on this basis, notably by Wiseman and Doan (9), who have often found phagocytosis of neutrophils within the reticulo-endothelial cells of the spleens in their cases. These observations require confirmation however. Phagocytosis of platelets in idiopathic thrombocytopenic purpura has been described only rarely.

The opposing view, that the various cytopenias might be due to a splenic "depression" or "inhibition" of the bone marrow, was first suggested by Rendu and Widal (1899) (10) and by Isaac (1912) (11). This view implied that the enlarged spleen inhibited formation of blood cells within the marrow and/or inhibited their delivery from the marrow to the peripheral blood. The implication was also present that not all cases of "splenic anemia" were hemolytic in type. Frank (1916)<sup>5</sup> accepted the thesis that over-production of a splenic hormone gave rise to certain cases of anemia by bonemarrow inhibition; and postulated the same mechanism to explain the neutropenia found in diverse cases of splenomegaly (*kala-azar*, typhus, Hodgkin's disease, cirrhosis of the liver.). Frank had already suggested that some circulating "toxin" was responsible for idiopathic thrombocytopenic purpura by inhibition of platelet formation from megakaryocytes in the marrow; but he did not state whether this "toxin" might originate in the spleen. (12). Minot, in 1917 suggested the possibility that idiopathic thrombocytopenic pur-

pura might sometimes be due to a splenic toxin which so affected the megakaryocytes that they were unable to produce platelets in normal fashion. He also discussed the possibility that "activity of the spleen" might affect not only the megakaryocytes but also, in other cases, the bone marrow erythrocytes and granulocytes, resulting correspondingly in anemia and neutropenia (13).

That idiopathic thrombocytopenic purpura is indeed the result of splenic hormonal inhibition of platelet formation from megakaryocytes has been reasonably well established (splenic thrombocytopenia) (14) for at least many cases. Splenic anemia due, not to increased hemolysis, but to inhibition of the erythrocytes in the marrow and cured by splenectomy has also been reported (15). In recent years, following the articles of Doan and Wiseman, many cases of splenic neutropenia and splenic pancytopenia have appeared in the literature, although a hormonal explanation for their pathogenesis has been accepted only occasionally (16). Splenic pancytopenia in which all the marrow elements are inhibited by an enlarged hyperactive spleen have been reported by Engelbreth-Holm (17), Dameshek (18) and Dameshek and Estren (18a). Whatever the mechanism, whether phagocytosis or inhibition, it is agreed that splenectomy is the only treatment of value.

Numerous observations indicate that the normal spleen has certain regulatory effects upon the bone marrow controlling the release of the various marrow cells into the circulation. Since it is probable that the passage of a cell from the marrow to the blood is a function of its maturity, the spleen may well control cell maturation within the marrow, and thereby its release. In the absence of such control (e. g. after splenectomy), granulocytic leukocytosis, thrombocytosis, and the appearance in the circulation of immature granulocytes and erythrocytes (Howell-Jolly bodies, nucleated erythrocytes) are common features. In view of the lymphocytosis following splenectomy, Singer, Miller, Dameshek (19), suggest a controlling influence by the spleen on lymphocytopoiesis as well.

Splenomegaly is found in numerous conditions. Whenever enlargement of the spleen occurs, the normal activities of the

spleen appear to become exaggerated, resulting in "hypersplenism". This occurs in conditions of totally diverse etiology, suggesting a functional disturbance induced in some obscure manner by the enlarged spleen. Hypersplenism has been found with splenomegaly in the following conditions:

Acute and subacute infections: Kala-azar, typhus, typhoid, measles, brucellosis, subacute bacterial endocarditis.

Chronic infections: Tuberculosis, syphilis, malaria.

Infection-like states: Rheumatoid arthritis, Boeck's sarcoid.

"Congestive splenomegaly": Cirrhosis of the liver, portal vein thrombosis, splenic vein thrombosis.

Disorders of Lipid Metabolism: e. g. Gaucher's disease.

Benign proliferation: Benign tumors and cysts.

Malignant proliferations: Leukemia, Hodgkin's disease, lymphosarcoma.

Idiopathic splenomegaly.

Those syndromes in which the etiology of the splenomegaly can be ascertained may be spoken of as "secondary splenic cytopenias". In many instances, the cause for the splenomegaly is obscure, and the picture may be described as "primary hypersplenism" or "primary splenic cytopenia". The particular variety of cytopenia has no relationship to the underlying cause for the splenomegaly; i. e. in *any* of these conditions, anemia, neutropenia, and thrombocytopenia may occur either singly or in various combinations, including splenomegaly; in both primary and secondary cases, removal of the spleen is usually followed by return of the blood values to normal.

These syndromes have been known for many years, but it is only recently that they have come into prominence. The "primary" types constitute the unexplained cases of splenomegaly with neutropenia, anemia, thrombocytopenia or pancytopenia. Certain instances of so-called "refractory" anemia fall into this group and are cured by splenectomy. Felty's syndrome, described in 1921, (20) is a form of cytopenia asso-

ciated with the splenomegaly of rheumatoid arthritis. The neutropenia considered so characteristic of kala-azar, Gaucher's disease, chronic malaria, cirrhosis of the liver, etc. is in all probability merely a manifestation of the splenomegaly of these disorders, and not of the disorder itself. The term, "Banti's Syndrome" to connote splenomegaly with cytopenia is obviously superfluous and incorrect since almost *any* splenomegaly, irrespective of its cause, may result in cytopenias. Banti's original conception of an orderly progression of splenomegaly, anemia and cirrhosis of the liver has not been supported by continued observations over the years.

During the past several years we have observed 28 patients in whom a diagnosis of hypersplenism was made, exclusive of cases of pure splenic thrombocytopenia (idiopathic thrombocytopenic purpura). These patients could be divided into three main groups:

1. Neutropenia with or without thrombocytopenia.
2. Pancytopenia in which the anemia was not hemolytic.
3. Pancytopenia in which the anemia was hemolytic.

This subdivision is admittedly artificial for, according to our concept, in all cases there is an overactivity of some function of the spleen. The factors which result in neutropenia in one case, thrombocytopenia in another, and pancytopenia in others, are quite unknown.

Clinically, the symptomatology corresponded to the particular cytopenia present. Patients with neutropenia complained of weakness, fever, recurrent infections, and polyarthralgia. Patients with anemia had weakness, pallor and fatigue. When the anemia was hemolytic, severe weakness, jaundice and fever were often present. Patients with thrombocytopenia complained of petechiae and ecchymoses; rarely, of more marked bleeding.<sup>1)</sup> In patients with pancytopenia, the symptoms were additive, although one group usually predominated.

On physical examination the spleen was always enlarged. In some cases the liver was also palpable. In two cases, en-

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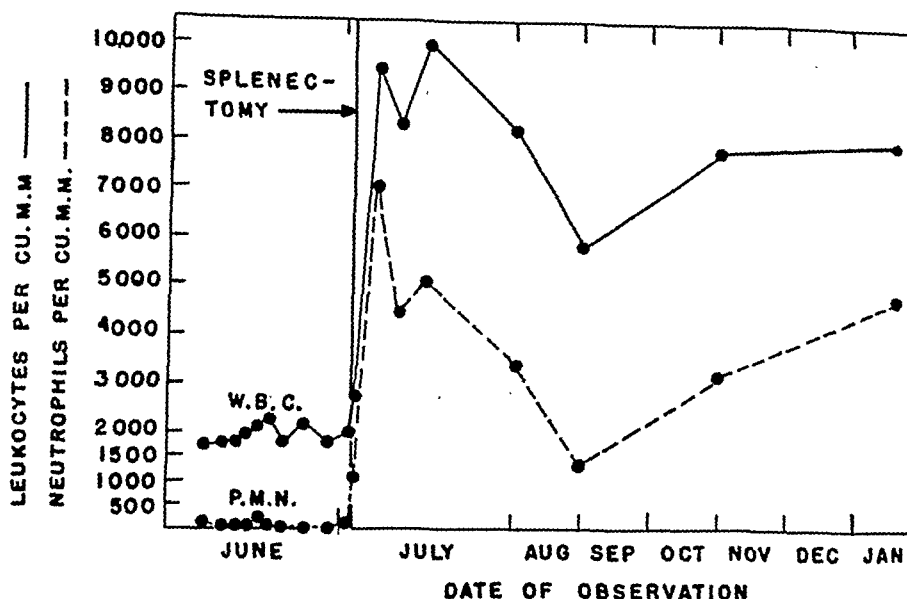
<sup>1)</sup> It should be recalled that patients with pure splenic thrombocytopenia were not included in this series. In them, of course, bleeding is a marked complaint.

larged lymph nodes showing non-specific hyperplasia on biopsy were present. Pallor, icterus, petechiae and ecchymoses completed the picture in the corresponding cytopenic states.

The prominent laboratory finding was the occurrence of some form of cytopenia despite adequate and often increased production of the involved cell in the bone marrow. The patients with neutropenia showed normal or increased numbers and normal development of granulocytes within the bone marrow. The patients with thrombocytopenia showed adequate or increased numbers of megakaryocytes, but with little platelet formation. The patients with anemia showed normoblastic hyperplasia in the bone marrow. This marrow picture was present even in those patients in whom the splenomegaly was due to some determinable underlying disease. Thus, in a patient with Gaucher's splenomegaly and pancytopenia who showed many Gaucher cells in the marrow, there was nonetheless an associated overproduction of granulocytes, megakaryocytes and erythrocytes. It was as if the cells normally produced were being prevented ("blocked") from entering the circulating blood with the result that they accumulated within the bone marrow.

The common denominator in these cases of variable etiology was the combination of (1) splenomegaly with, (2) a "full" marrow, and (3) an "empty" blood. Despite the various cytopenias in the blood, the marrow showed well marked hyperplasia with large numbers of the various types of cells. Given these findings, the possibility of hypersplenism required consideration. In each case, it was necessary to exclude as far as possible, certain alternative diagnoses. Infiltration of the marrow by leukemic or other foreign tissue, and myelosclerosis, were ruled out directly by marrow examinations. Malignant splenomegaly specifically leukemia or lymphosarcoma, — could almost always be eliminated by marrow studies, and at times by biopsy of enlarged lymph nodes (when present.) However, it must be realized that even with the most careful studies, an occasional case of malignant splenomegaly with symptomatic hypersplenism remained completely undiagnosed until splenectomy had been performed. Such a finding occurred in two of our series of cases.

## CASE M.C. PRIMARY SPLENIC NEUTROPENIA

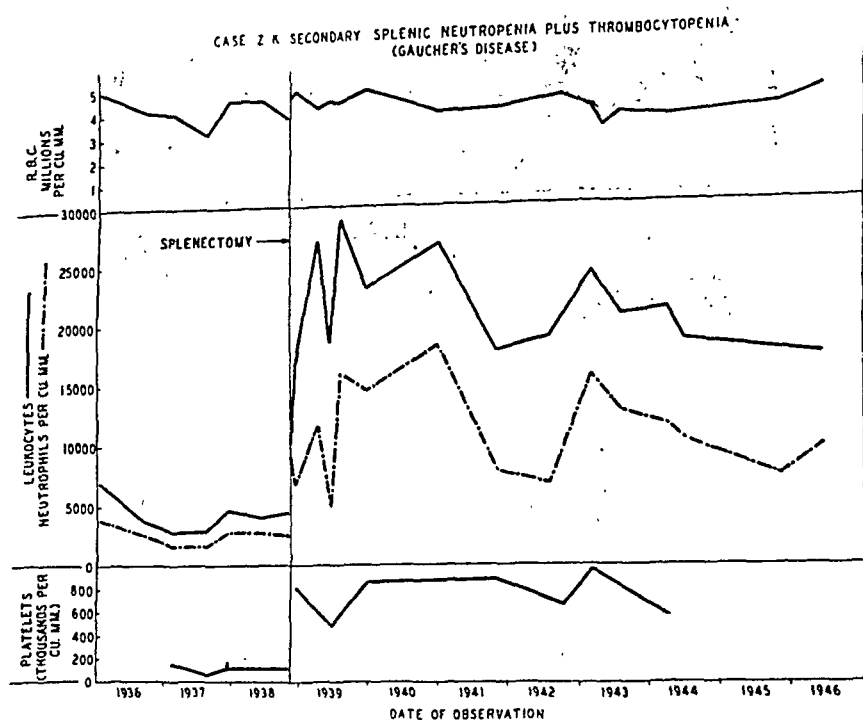


Case D.P. Primary splenic neutropenia. Cure by splenectomy. (Figure 1).

A 42 year old woman had a history of influenza and pneumonia twice in six months, recurrent polyarthralgia, and increasing weakness and weight loss for two years. Physical examination revealed moderate splenomegaly as the only positive finding. The white cell count was 1,550 per cu.mm., with 330 neutrophils (22 %) and 770 lymphocytes (48 % per cu. mm.) The red cell and platelet counts were normal. The bone-marrow, despite the neutropenia in the circulating blood, showed increased numbers of granulocytes, with normal development; and normal erythro-and-thrombopoiesis. Splenectomy was performed, and the spleen, which weighed 510 grams, showed nonspecific hyperplasia of both pulp and follicles. Phagocytosis of neutrophils was not observed. Immediately after operation the white cell count was 5,100 with 3,400 (64 %) neutrophils; a year later, it was 9,800 with 6,000 neutrophils (62 %). The symptoms disappeared and the patient has remained well for three years.

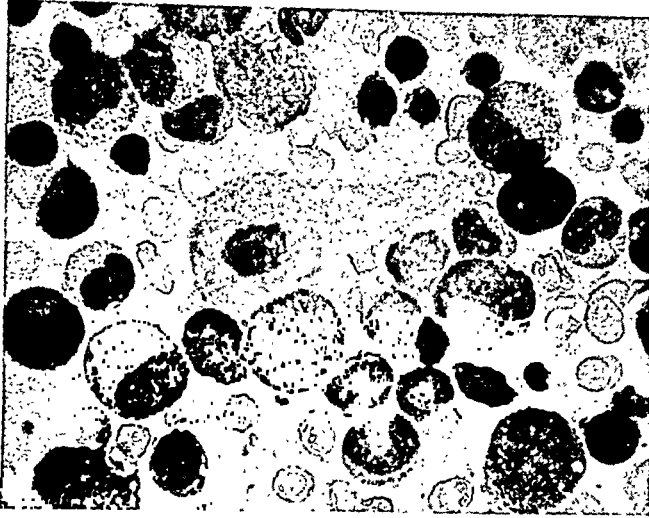
*Comment:* Marked neutropenia was present in the circulating blood despite good production in the marrow. Removal of the nonspecifically hypertrophied spleen was followed by a return of the blood values to normal and a disappearance of

symptoms. The enlarged spleen had apparently inhibited release of granulocytes from the marrow (and of lymphocytes from the lymphatic tissue). Removal of the spleen, by eliminating this "block" resulted in clinical and hematological cure.



*Case Z.K.: Splenic pancytopenia with nonhemolytic anemia, secondary to Gaucher's splenomegaly. Cure by splenectomy. (Figure 2).*

Splenectomy was recommended in a six year old, Jewish boy because of marked difficulty in locomotion and a well defined hemorrhagic diathesis. The latter was due to thrombocytopenia, one of the features of a generalized reduction in blood cells (i. e. pancytopenia). The marrow showed numerous Gaucher cells, but the production of red cells, granulocytes, and megakaryocytes appeared to be normal. The spleen weighed 1,300 grams and showed Gaucher's disease and generalized hyperplasia. The pre- and post-operative blood counts are listed below and depicted graphically in Figure 2.

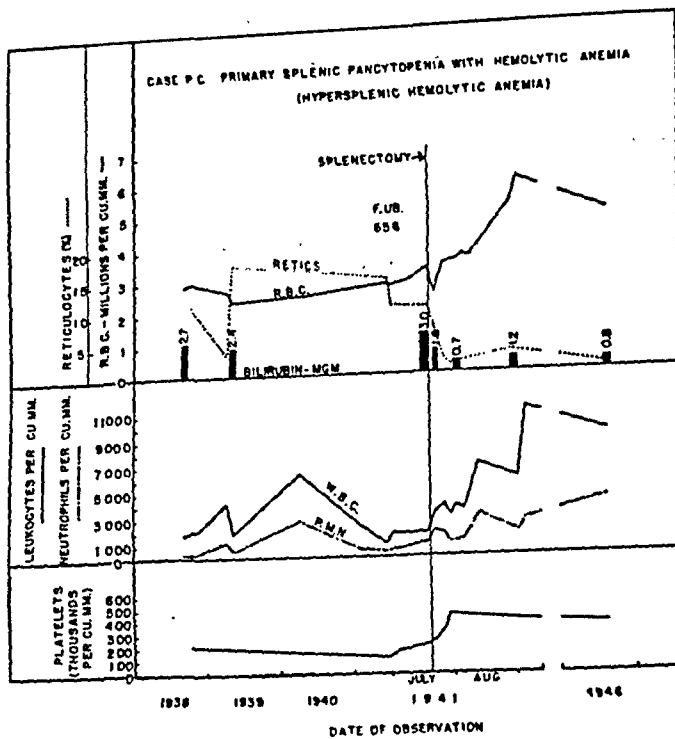


*Blood Counts.*

	Pre-operative	Post-operative	8 years later
W. B. C. ....	2,800	18,300	17,200
P. M. N. ....	1,600 (58 %)	5,500 (31 %)	9,600 (56 %)
Lymphs. ....	ca. 1100 (40 %)	9,700 (53 %)	6,400 (37 %)
R. B. C. ....	3.7 M	5.1 M	4.7 M
Plts. ....	176,000	810,000	incr. on smear

Eight years after splenectomy, the patient had no complaints referable to the blood, although the fundamental disorder, Gaucher's disease, had resulted in changes in the bones and enlargement of the liver.

*Comment:* Although Gaucher cells were numerous in the marrow, the development of blood cells was more than adequate, yet the blood showed reduced numbers of red cells, platelets and granulocytes. There was no evidence of excessive hemolysis. After splenectomy, the blood counts became normal and then granulocytosis and lymphocytosis occurred. This is an example of "secondary" hypersplenism in which the spleen, enlarged by Gaucher's tissue, had the usual inhibitory effects of an enlarged spleen on the marrow. Its removal was followed by hematologic cure.



*Case P.C. Primary splenic pancytopenia with hemolytic anemia. Cure by Splenectomy (Figure 3).*

A 55 year old man with three years of unexplained fever, pallor, slight icterus, weakness and hepatosplenomegaly, consistently showed pancytopenia. Sudden weakness and an increase in icterus suggested an increase in hemolysis. Blood studies showed white cells 1,350; neutrophils 620 (46 %); lymphocytes 510 (38 %); red cells 2.58 million; platelets 109,000; reticulocytes 10—20 %; serum bilirubin 7.2 mgm. indirect, 2.8 mg. direct. The daily fecal urobilinogen excretion was 8 times normal. The bone marrow showed increased granulopoiesis and marked normoblastic erythropoiesis. Platelet formation from the megakaryocytes was greatly reduced.

At operation a spleen weighing 1,000 grams and showing non-specific hyperplasia with slight fibrosis and hemosiderosis was removed. The patient improved rapidly, with a progressive rise in all the blood values (Figure 3) to normal values. Five years after splenectomy, the blood studies were as follows: White cells 9,500, neutrophils 4,350 (46 %); lymphocytes 2,900 (31 %); red cells 4.88 million, platelets 461,000.

*Comment:* In this case, idiopathic enlargement of the spleen was apparently the cause of a chronic remitting hemolytic anemia with neutropenia and thrombocytopenia. Most hemolytic processes are accompanied by a total marrow reaction:

i.e. neutrophilic leukocytosis and thrombocytosis (or normal platelet counts.) The picture of a pancytopenia accompanying a hemolytic process is not well known, but we have now seen at least eight cases, which we have designated as "hypersplenic hemolytic anemia". In these cases, the spleen appears to be the sole cause of the increased hemolysis. The spleen, which is already destroying large numbers of red cells, also apparently prevents the delivery from the marrow of normal numbers of granulocytes and platelets. This is a case of splenic pancytopenia in which the anemia was hemolytic in type.

### *Summary.*

The spleen probably numbers, among its many functions (reservoir, erythrocytolytic, hematopoietic), the function of regulation of the bone marrow by hormonal means. This regulation acts on production and/or delivery of granulocytes, erythrocytes and platelets from the marrow to the blood. Under certain conditions, notably when the spleen becomes enlarged, *whatever the reason*, these hormonal functions become exaggerated. The result of excessive regulation of cell production and delivery is inhibition, so that neutropenia, thrombocytopenia, anemia, or pancytopenia result. In some cases, the spleen at the same time destroys red cells excessively, and a hemolytic component becomes apparent.

The necessary conditions for the diagnosis of hypersplenism are (1) unexplained cytopenias in the blood, (2) splenomegaly, and (3) normal or increased cellular components in the bone marrow. Except in cases of pure splenic thrombocytopenia, (idiopathic thrombocytopenic purpura) the spleen is enlarged. The splenomegaly may be due to a variety of causes including rarely, Hodgkin's disease, leukemia and sarcoma. In every case of suspected hypersplenism, malignant splenomegaly must be ruled out as far as possible. Even with the most careful precautions, leukemia may occasionally remain latent until after splenectomy.

If the diagnosis of hypersplenism is correct, splenectomy may be expected to be curative of the hematologic condition and the corresponding symptoms in some 80 % of cases. In certain cases,

especially those with severe neutropenia or hemolytic anemia, the operation may be life-saving.

The concept of hypersplenism, an old one born in the late 1800's and nourished largely in Europe in the early 20th century, is reemerging as a means of explaining many bizarre cases of splenomegaly with cytopenia; and as an approach to the treatment of certain apparently hopeless cases of so-called "refractory" anemia.

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## STUDIES ON INFLUENZA MADE DURING TWO EPIDEMICS IN BOSTON

By  
*Maxwell Finland, M. D.*

When Dr. Jersild extended the invitation to contribute to this commemorative volume I felt indeed honored and delighted. My personal thanks are due to Dr. Meulengracht for the generous hospitality for which he is well known and of which I was one of the many recipients during a visit to Copenhagen some years ago. Together with my colleagues at the Thorndike Memorial Laboratory I am likewise very much indebted to Dr. Meulengracht for his instructive and stimulating, though much too infrequent visits here. We are also very grateful to him for sending to us from his clinic some of the very fine young men with whom it has been our greatest pleasure to be associated and who have left us with the greatest admiration for our Danish colleagues and for the quality of their work.

In seeking a topic for this contribution, it seemed appropriate to present a resume of studies made during an epidemic of influenza B infections that occurred in Boston in December 1945 at a time when Dr. Jersild was visiting at our laboratory. Like the author, Dr. Jersild himself fell ill with this infection and contributed some of his blood for some of the serological tests upon which many of the studies were based. He, unfortunately, could not stay long enough to observe the results of the studies that were carried out with the materials collected during that epidemic. Before presenting the results of these studies, it might be of interest to summarize briefly some findings that were obtained in the winter of 1943—44 during the height of an epidemic of influenza A and during several weeks after that epidemic had subsided.

*Results Obtained During the Winter of 1943-44.*

*Isolation of Viruses.* Influenza viruses were isolated with great ease both during and after the height of the earlier epidemic. Strains of influenza virus were isolated from throat washings obtained from patients acutely ill with the characteristic symptoms of influenza and also from the lungs of some fatal cases of pneumonia. The successful isolations were made from filtered and unfiltered materials both by the intranasal inoculation of mice and also by inoculations directly into the allantoic sac in developing chick embryos and these viruses could then be readily propagated by further passages either in mice or through allantoic inoculations of embryonated eggs.

*Identification of Strains.* The reactions of viruses obtained during the height of this epidemic and the antibody response to characteristic infections occurring at that time indicated that the epidemic cases were caused chiefly by strains of influenza A and these viruses gave reactions which were similar to those obtained with the standard PR8 strain. The post-epidemic cases, on the other hand, were atypical not only with respect to the viruses which were isolated during the acute stage of the illness, but also in their antibody responses. The latter virus strains were classified, after considerable study, as influenza A, though they differed markedly from the standard PR8 strain. The serum of the patients who were ill with the typical symptoms of influenza 3 weeks or more after the peak of the epidemic prevalence, however, failed to show any antibody response either to their own strains or to the standard PR8 strain. No evidence of infection with influenza B was obtained in any of the cases studied either during or after this epidemic.

*Serologic Results in Uncomplicated Cases of Clinical Influenza and Other Simple Respiratory Infections.* In the sera of persons who gave a characteristic history of clinical influenza during the epidemic of 1943, significant titers of antibodies to the PR8 strain of influenza A were demonstrated either by the inhibition of chicken cell agglutination or by complement fixation, and these antibodies persisted sometimes for as long as 12 weeks after the onset of symptoms. Such significant titers were not demonstrated during the same period in persons who

either denied having any symptoms of acute respiratory infections or who had symptoms which were considered to be those of the "common cold" and not of influenza. It seemed that in this outbreak at least there was a very close correlation between clinical symptoms and evidence of influenza A virus infection in those who had respiratory infections during the height of the epidemic and this was not true after the epidemic had subsided.

*Findings in Patients with Pneumonia.* Of particular interest during this epidemic also were the high titers of antibodies to influenza A (the PR8 strain) that were demonstrated in severe cases of bacterial pneumonia which occurred during and shortly after the epidemic and in which there was an antecedent history of symptoms characteristic of clinical influenza. These findings and the isolation of influenza A virus from the lungs of three fatal cases of pneumonia suggested that the occurrence and severity of pneumonia in such cases was related to the antecedent infections with influenza virus. The most frequent organisms obtained in the pneumonias which followed influenza were pneumococci of various types and *Staphylococcus aureus*. No significant bacterial pathogen could be recognized in some of the pneumonia cases including a fatal one in which a virus was recovered from the lung. Both *Staphylococcus aureus* and hemolytic streptococcus were obtained from lungs of one of the other fatal cases and type I pneumococcus was cultured from the lungs in a third case which yielded influenza A virus.

#### *Results Obtained During the Epidemic of December 1945*

*Virus Isolations.* The studies made during the winter of 1945—46 brought out some findings that were similar to those of the previous epidemic but there were many other points of difference. In the first place, there was considerably greater difficulty in isolating strains of virus from throat washings even early in the course of the disease. This difficulty has been commonly experienced by other workers where influenza B viruses were involved. In this epidemic influenza virus could be isolated only when infected materials were injected either into the amniotic cavity or directly into the embryo of the developing hen's egg and several blind amniotic or embryonic passages were often required before evidence for the presence of virus could be ob-

tained. Even after virus in appreciable titer was obtained in this manner and demonstrated in allantoic fluid, further passage by allantoic inoculation often resulted in the loss of the virus. Eventually, however, all of the strains could be adapted to growth in allantoic fluid by careful adjustment of dosage and by repeated passage.

In this manner virus was obtained on one or more attempts from the throat washings of 9 of 11 patients who gave serologic evidence of infection with influenza B. Influenza viruses could not be isolated on repeated attempts from any of the cases in which there was serologic evidence of infection with influenza A virus. Mouse inoculation by the intranasal route seemed to be helpful in some instances in establishing the virus more rapidly by subsequent passage of lung suspension in the amniotic sac of chick embryos. Direct mouse to mouse passage, however, resulted in loss of the virus and no strain could be established in this manner. In some instances, however, it was possible also to obtain viruses by one or two preliminary passages in mice and subsequent allantoic inoculations in chick embryos.

*Identification of the Strains of Virus.* All of the viruses that were isolated in the epidemic of December 1945 were shown serologically to be influenza B. However, there was evidence from agglutination-inhibition tests and from neutralization tests in chick embryos that two antigenically different strains were involved: one of them was closely related to the American Lee strain and the other differed antigenically from that strain, but resembled the Australian BON strain.

*Types of Cases Studied Serologically.* Serological studies were made in several groups of individuals as follows: 1.) Typical cases of clinical influenza in boys and girls aged 10 to 17 years. They were all pupils of the same school in Needham, a suburb of Boston where over one-half of the children were absent during the middle of December because of influenza. 2.) Family contacts of these children, including their parents and siblings. Some of these contacts had typical influenza, others had symptoms resembling the common cold and still others were free of infections. 3.) Members of the hospital and laboratory staff some of whom had symptoms of acute respiratory illness and others who did not have any respiratory infection, but were studied

as controls. 4.) Patients with clinical influenza or other simple respiratory infections but without evidence of pneumonia who were admitted to the regular medical wards of the hospital between December 1945 and early March 1946. 5.) Patients admitted to the hospital during this same period who had clinical and X-ray evidence of pneumonia.

*Results of Serological Tests in Typical Cases of Influenza from the School Epidemic in Needham.* The typical cases of clinical influenza in Needham all had the symptoms and other findings usually associated with this disease. Their illness was characterized chiefly by malaise, fever of 101 to 104° F., muscle and joint aches, slight soreness of the throat without physical evidence of angina, slight photophobia and conjunctival injection and little or no coryza. The lungs of those examined were essentially clear except for occasional musical rales. Serums obtained from these typical cases of clinical influenza, with three exceptions, yielded evidence of infection with influenza B by a significant rise in titers of antibodies against the Lee strain and/or one of the epidemic strains but not against the PR8 strain of influenza A. The three exceptions who failed to show any rise in antibodies to either influenza A or B were all members of the same family, and were the only ones who were ill in that family. The symptoms in these three cases were quite similar to those of the patients who gave serologic evidence of influenza B infection.

Some of the cases in Needham showed a rise in antibodies when tested with two strains of influenza B recently isolated from other cases in Boston, but failed to show a rise in the same sera when tested with the Lee strain of influenza B and with a strain isolated from one of the cases in Needham. The two Boston strains were later shown to resemble the Australian BON strain of influenza B. In no instance was a rise in influenza A antibodies demonstrated in this group of patients.

*Serologic Findings in Family Contacts of School Children with Proved Influenza B Infection.* Among the family contacts of the serologically proved cases of influenza B there were 4 who had symptoms that resembled those of the common cold with coryza as an outstanding feature and without fever. There were 4 others who had low-grade fever without respiratory symptoms but with nausea, vomiting and diarrhea as the predominating symptoms.

In none of these 8 patients, nor in any of the healthy family contacts of the proved case of influenza B was any significant rise in antibody titers demonstrated either against any of the strains of influenza B or against the PR8 strain of influenza A.

*Evidence of Two Types of Infection.* Both influenza B and influenza A infections were found to be prevalent among the cases of uncomplicated respiratory infections that were studied at the Boston City Hospital. Influenza B was shown by the virus isolations and by the serological tests to be responsible for the major outbreak that occurred in December 1945. No cases proved to be due to influenza B were encountered after the first week in January. Cases proved serologically to be influenza A were encountered almost entirely after the middle of January. Two cases were observed in which there was definite serologic evidence of consecutive infections first with influenza B and followed a few weeks later by influenza A infection. There was also some evidence of symptomless infections with viruses of both types.

*Correlation of Serological and Clinical Findings.* Almost all of the patients in whose sera a rise in specific antibodies to one or another of the influenza viruses was demonstrated had respiratory and systemic symptoms which were characteristic of clinical influenza. These varied in duration and severity. Similar symptoms were noted during the same period in a few other individuals whose sera failed to show such a rise. However, the great majority of the patients who failed to show a rise in influenza antibodies either had an illness which was more like that of the common cold or had predominantly gastrointestinal symptoms. The small group of hospital and laboratory workers who were observed throughout the period of study and who had no evidence of respiratory infection during the same period all failed to show serologic evidence of infection with either influenza B or influenza A.

*Serologic Findings After the Epidemic.* In order to get some idea as to whether a retrospective history of respiratory infection during the epidemic might be reflected in a high influenza antibody titer a few weeks later, single specimens of sera were obtained a few weeks after the last serologically proved case of influenza were observed. Most of these individuals were young adults hospitalized for illnesses other than acute respiratory in-

fections and others were members of the hospital staff. Some of these patients had illnesses which, from the history, could be characterized as clinical influenza and others had previously had respiratory symptoms that resembled the common cold, but many had no history of respiratory infection. In this group there was a comparatively large number of individuals who showed somewhat elevated titers of agglutinin-inhibition of PR8 strain without corresponding elevations in the titers of complement fixation with the same strain. There were few instances of similarly elevated titers of agglutinin inhibition of the Lee strain, but those that showed such elevated titers also had complement fixation titers with this strain that were higher than average. Except for the somewhat greater frequency of high agglutinin inhibition titers with both PR8 and Lee in persons giving a recent history of clinical influenza there seemed to be no significant occurrence of elevated titers in the patients with history of common cold and in those having no history of respiratory infections.

*Serologic Findings in Patients with Pneumonia.* The findings in the patients with pneumonia were of particular interest. These cases included all the various types of bacterial pneumonia usually seen in this clinic. Most of them were classical lobar pneumonias due to specific types of pneumococcus and in some of them positive blood cultures were obtained. There were also atypical pneumonias due to pneumococci and other pyogenic organisms, particularly *Staphylococcus aureus* but there were some patients from whom no significant bacterial agent could be obtained from cultures of the sputum or blood. A total of 69 patients were studied and, from the results of the serological studies, they fell into three distinct groups, each of which will be discussed separately.

*Pneumonias Showing a Rise in Antibodies for Influenza B.* First there was a group of 11 patients all of whom showed a significant rise in antibodies for influenza B similar to the rises found in uncomplicated cases of influenza. There was an illness which, from the history, was considered to be clinical influenza preceding the onset of pneumonia or beginning at about the same time in all but one of these cases. In these patients, the first symptom of the clinical influenza occurred between No-

vember 30 and January 11 in every instance. The onset of the pneumonia, as far as could be determined from the history, occurred on the same day in three cases and from 1 to 10 days later in the others.

*Pneumonias with Serologic Evidence of Recent Infection with Influenza B.* There was another group of 25 patients in whom the findings were similar in most respects to those found in the preceding 11 patients. They differed only in that the history of the antecedent influenza in these cases occurred usually a week or more prior to the time when the first blood sample was obtained. In all of these 25 cases the titer of antibodies for influenza B in the initial serum was significantly elevated and corresponded to the titers found in the convalescent sera of the 11 patients with pneumonia just mentioned and also in the cases of uncomplicated influenza which showed a typical rise in influenza B antibodies. A history considered to be that of clinical influenza was obtained in 19 of these patients; two others had an illness which was more like the common cold, while no history of an antecedent illness distinguishable from the pneumonia was elicited in the 4 remaining patients. In this group of cases, too, the onset of the initial illness occurred between December 3 and January 12. The interval between the onset of influenza or the cold and the pneumonia was 7 days or less in 12 of these cases and from 8 to 14 days in 8 others.

*Pneumonia Without Evidence of Influenza Virus Infection.* Finally, there were 33 patients in whom no serologic evidence of recent infection with either influenza A or B could be demonstrated. A large proportion of the antecedent illnesses in this group as judged from the histories resembled common colds, but there were 12 patients in whom these preceding illnesses could be classified from the histories as clinical influenza. The pulmonary lesions and other findings in this group of cases were generally similar to those found in the two previous groups. The failure to demonstrate evidence of influenza virus infection in this last group of cases was not due to initially elevated titers. The titers of influenza A and B antibodies in this group of cases were similar to those found during the acute phase in the patients with proved influenza A or B virus infections, with or without complicating pneumonias.

*Evidence of Influenza A Infection in Patients with Pneumonia.*

In addition to these cases of pneumonia which showed evidence of infection with influenza B, there were 3 patients who had serologic evidence of influenza A. In these 3 cases the symptoms of clinical influenza began between January 25 and February 2 and the pneumonia began between February 2 and February 12. In one of these cases no significant bacterial pathogen was isolated and the patient clinically resembled primary atypical pneumonia, though cold agglutinins did not develop. The other 2 were typical cases of lobar pneumonia, one due to type 5 and the other to type 4 pneumococcus.

It was thus seen that about one-half of the cases of pneumonia that occurred during the period of epidemic prevalence of influenza B, irrespective of the clinical character of the pneumonia or of the bacteriologic findings, yielded serologic evidence of recent infection with influenza B virus. Likewise the great majority of patients in whom serologic evidence of influenza B infection was obtained had an illness which was characteristic of clinical influenza. That illness began either about the same time as the pneumonia or within a few days previous to the onset of pneumonia. Likewise evidence for the occurrence of pneumonia following influenza A infections was found in some cases.

Details of the studies mentioned in this communication are published elsewhere. The serological studies and the virus isolations were carried out largely with the assistance of Mildred W. Barnes. The clinical observations were made with the collaboration of Dr. Bernardo A. Samper during the winter of 1943—44 and with Drs. Manson Meads and Edwin M. Ory during the winter of 1945—46. Some of the studies on the identification and antigenic relationships of the virus in the latter outbreak were carried out with the assistance of Dr. Herbert R. Morgan.

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## OPERATIVE TREATMENT OF ABDOMINAL OBESITY, ESPECIALLY PENDULOUS ABDOMEN

By  
Jens Foged, M. D.

As in the Scandinavian countries this form of treatment appears to be employed but very little, it seems appropriate on the basis of my own experiences and data recorded in the literature to give a brief description of the clinical aspects of the lesion and the methods for its operative correction.

Historically, Kelly (1899) seems to have been the first to adopt an operative therapy in pendulous abdomen. Subsequently several operative methods have been advanced, the more important of which will be outlined later on. Küster has attempted to classify the different types of pendulous abdomen and abdominal obesity.

The term *venter propendens* is applied to an abnormal, diffuse, excessive development of the subcutaneous adipose tissue of the abdomen (pot-belly) or to an increase in the panniculus adiposus localized to the declive parts, hanging down over the symphysis and groins — sometimes over the upper part of the hips too — as an apron of adipose tissue covered with distended skin. This is a condition generally designated as pendulous abdomen which will be dealt with in the following. Not infrequently *venter propendens* is complicated by prolapse of the abdominal wall (*venter extentus*), and this prolapse may be relatively diffuse (*venter extentus globus s. fusus*, ball-belly, frog-belly) or more localized usually to the area round the midline (*venter extentus medialis*).

### *Etiology and Pathogenesis.*

The diffuse abdominal obesity appears to follow the rules for *adipositas universalis*, to which it is near related. Also the more localized pendulous abdomen is encountered more often

in obese persons' (in 25 out of the 35 patients in our material), but sometimes it is seen in rather thin individuals as a more or less flaccid fold of skin and adipose tissue hanging down over the symphysis (4 out of 35 patients). A typical feature of pendulous abdomen, however, is its development in obese persons whose integuments are flabby after one or more reducing cures, which may make a part of the subcutaneous fat disappear but, as a rule, are unable to cause any change in the metabolism of the more declive part of the hanging fold — presumably because the arterial supply of this structure is very slight. At any rate, of our 35 patients 30 had gone through one or — more often — some energetic reducing cures without any particular effect on the pendulous abdomen. On the contrary, this condition became rather more pronounced on the background of the reduced adiposity elsewhere. Undoubtedly some constitutional factor is asserting itself in the development of this condition. Thus pendulous abdomen is decidedly a female disease even though it may occur in men too. All the 35 patients in the present material were women.

Furthermore, pendulous abdomen is seldom an isolated phenomenon of localized accumulation of fat in these patients. Most often it is combined with mammary hypertrophy or mastoptosis (23 out of 35 patients) or wads of fat in the nape, dorsal region, flank, or on the medial aspect of the thigh or knee (25 out of 35 patients).

According to our material, heredity may hardly play any rôle. Further, it is uncertain whether racial factors are of any significance. As in adipositas in general, some cases are due to endocrine affections.

It has been claimed that many parturitions will dispose to pendulous abdomen. Theoretically, however, there appears to be no reason for this assumption; and, at any rate, this is not confirmed in our material. On the other hand, we have to assume that parturitions may dispose to venter extensus.

### *Clinical Aspects.*

As presumably the clinical features of pendulous abdomen are well known, it will suffice merely to recapitulate them briefly.

Most often the patient is a middle-aged woman. In our material of 35 cases the age distribution between 25 and 68 years has been: 10 under 40 years, 2 over 60, the remaining 23 patients between 40 and 60 years. As a rule the development of the affection lasts a good many years: among our patients, on an average, 10—15 years. Only two patients stated that their lesion had developed more rapidly: in 6 months and 2 years, respectively.

As a rule the patient has gone through a number of reducing cures, accentuated by abundant thyroid medication, trying also all other conservative measures — massage, corset, abdominal belt — without satisfactory result.

She now complains of her large hanging belly, which is heavy and inconveniencing, sometimes also painful, impeding her gait and motions, making it impossible for her to take part in gymnastics or any sport. Not infrequently, intertrigo arises in the skin folds over the symphysis and groins. She complains of her “impossible” shape, which annoys her cosmetically. She would not dare to show herself in a public bathing establishment, she has difficulty in getting any clothing that will fit her, and she can never be as well-dressed as her more well-shaped friends. All this gives her a complex of inferiority and, furthermore, her pendulous abdomen will often make a normal sexual life rather difficult or impossible.

### *Symptoms.*

The complaints most often recorded in all 35 cases are as follows:

*Entirely physical symptoms* (pain, heaviness, intertrigo, hampered movements, etc.): 32 cases.

*Occupational inconvenience*: 24 cases. This group is made up chiefly by housewives, waitresses, clerks and singers. On the whole, it is obvious that pendulous abdomen usually will make the patient unserviceable for any occupation in which she will have to appear *coram publico*.

*Sporting inconveniences*: 12 cases.

*Clothing, cosmetic or esthetic inconveniences*: 30 cases.

In addition there is a number of symptoms from other affections often concurrent with pendulous abdomen, e.g., adi-

positas universalis, mammary hypertrophy or mastoplosis, wads of fat elsewhere, arthrosis of the knee, varicose veins, and arterial hypertension.

### *Physical Examination.*

The objective symptoms show gradual transitions between pendulous abdomen combined with diffuse venter extensus to isolated pendulous abdomen in all sorts of degrees — from small flabby folds of skin and adipose tissue to enormous accumulation of facts hanging as a thick and heavy apron and, in its most severe form, reaching down to the knees.

It is easy to understand that pendulous abdomen may be a very troublesome affection that finally drives the patient to seek operative treatment. This is illustrated very well by the following typical case history.

### *Case Record.*

Woman, 60 years old. Adm. to Dept. A 2/2—9/3/41. Record No. 826/41).

*Diagnosis:* Pendulous abdomen; Arthrosis of knees; Adipositas.

Past history of good health. 4 parturitions. During the past 30 years the patient has been suffering from adipositas, for many years from pendulous abdomen too. Last year, a reducing cure made her loose 25 kg. Under this treatment, her pendulous abdomen became more pronounced, and since its symptoms have troubled her increasingly in the form of heaviness, dragging, impediment of motions, difficulty in keeping clean, intertrigo, difficulty in getting clothing that fits her.

Lately it has been troublesome for her to move about, and now she is unable to attend to her work as owner of a small restaurant. She has tried to use an abdominal belt, but she cannot stand it.

Physical examination: Nutrition far beyond medium. Weight: 105 kg. Height: 157 cm. Of the findings obtained, only the following are of interest: Abdomen exceedingly obese; its declive parts — from flank to flank, a little below the umbilicus — hanging like a thick mat (15—20 cm. in thickness) down over the anterior aspect of both thighs, covering them completely and reaching almost to the knees. A deep longitudinal groove in this fat apron leads up to the umbilicus (Fig. 1). Palpation through this enormous blanket of adipose tissue is impossible, and thus it cannot be decided whether it contains any intestinal loops. Still, roentgenography after a contrast meal shows that this is not the case.

*Treatment:* As any conservative treatment in this case is con-

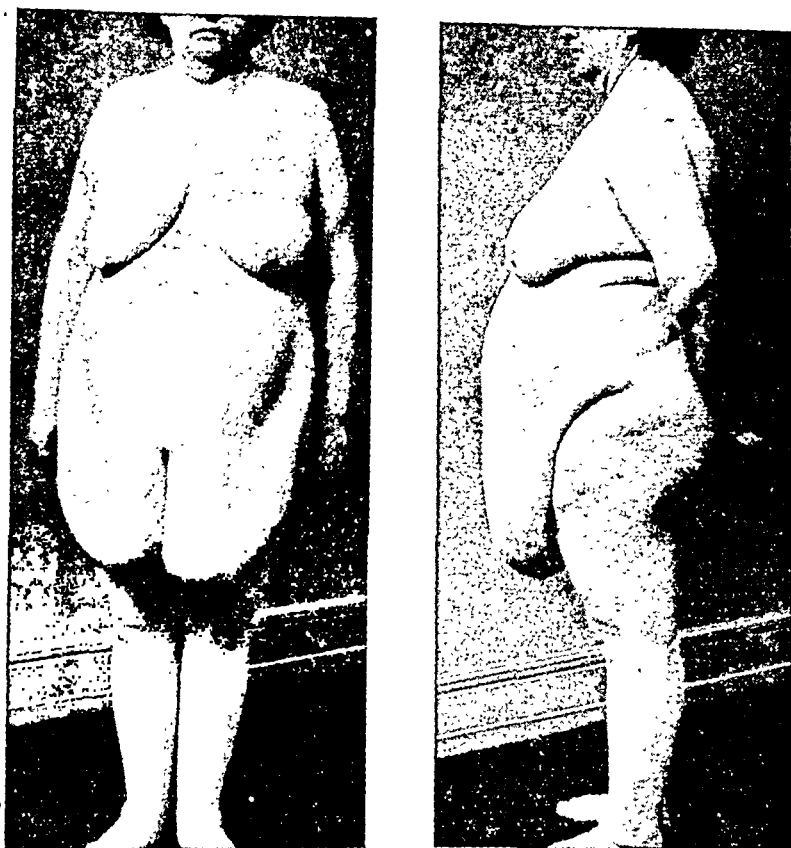


Fig. 1.

sidered hopeless, and the symptoms are so severe, operative treatment is decided on, as the risk implied by this treatment is no greater than justifiable.

From 15/2/47, under ether anesthesia: lipectomy of the abdominal wall, through a large transversal-oval incision the excessive skin and subcutis (unto the fascia) were removed, altogether 6500 g. The flabby fascia was duplicated transversely to the extent of about 10 cm.

The postoperative course was uncomplicated.

*Reexamination;* on 20/2/47: Apart from her persistent obesity, the patient is feeling well and satisfied, the symptoms connected with the pendulous abdomen are all gone. Since the operation the patient has been able to do her usual work in the restaurant.

The scar from the operation is practically not noticeable. In spite of the largeness of the abdomen, which is covered with an enormous panniculus adiposus, there is no suggestion whatever

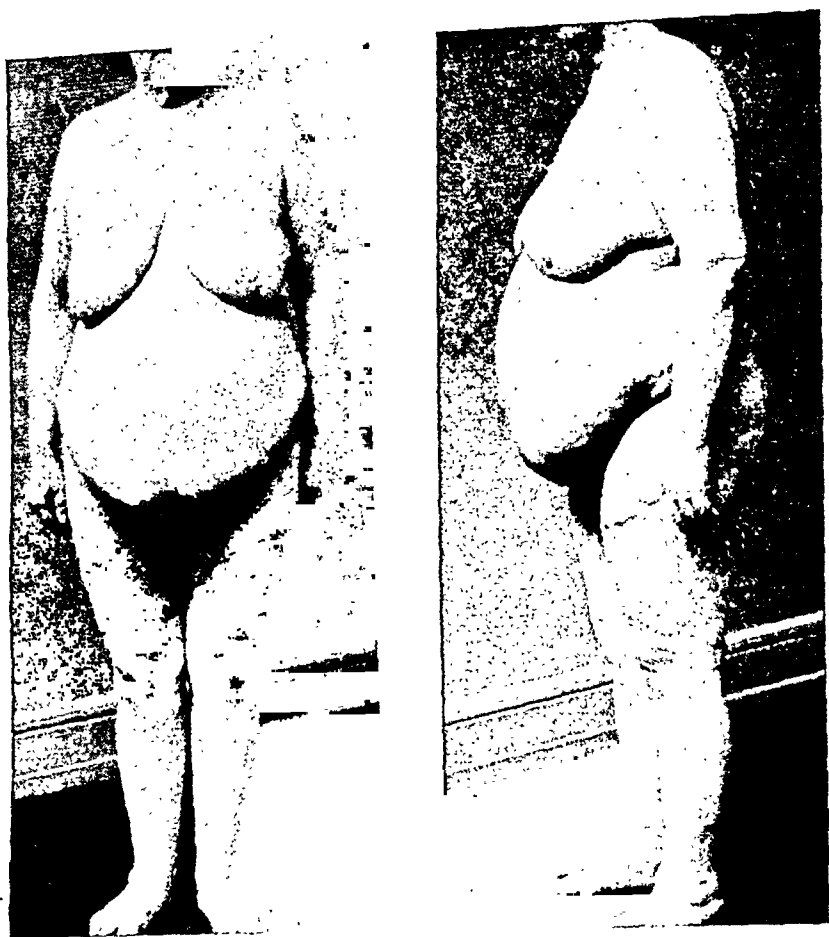


Fig. 2.

of a tendency to pendulous abdomen — as is plainly evident from the photo taken at that time (Fig.2).

In pendulous abdomen and venter extensus two forms of treatment are possible, conservative and operative. Even though here we will deal in particular with the operative treatment, the conservative methods are to be touched upon too, all but briefly.

Prophylactically, the frequency of pendulous abdomen may presumably be lowered by reducing measures instituted sufficiently early. In cases where pendulous abdomen already has developed, the conservative treatment consists in reducing diet, massage, Swedish gymnastics and proper bandaging. In cases of isolated pendulous abdomen, as is evident from our material,

reducing measures usually fail. Still, as a rule, such measures should be tried, as they constitute a desirable preoperative prophylaxis in the usually very obese patients.

Undoubtedly massage and Swedish gymnastics are of some value in these cases, but experiences are wanting as to the therapeutic results.

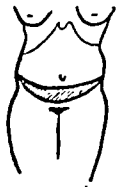
As is well known, the palliative treatment with bandage, elastic corset or abdominal belts is employed extensively, and in many cases it undoubtedly will be able in some degree to medigate the symptoms.

In weighing the indications for operative treatment, consideration has to be paid both to the severity of the symptoms in the given case and to the operating risk. As these patients most often are middle-aged — and not infrequently older — obese and flabby women with dissended abdomen, sometimes with myocardial degeneration, obstipation and varicose veins, and as the operation still involves the removal of a considerable portion of tissue, this measure implies a not quite insignificant risk.

As the operative treatment hardly may be said to be a matter of emergency, it will be imperative correctly to select the patients suitable for such treatment with a special view to their general condition, function of capacity of the heart (electrocardiography + roentgenography), peripheral vessels (blood pressure, arteriosclerosis, varices), intestinal function and kidney function. A particular indication is found in patients with pendulous abdomen in whom this affection will make it difficult to perform an otherwise indicated laparotomy on the lower part of the abdomen. In such cases we consider it quite appropriate to perform lipectomy at the same time — as we have done in 2 cases. The same applies to cases in which operation has to be performed for ventral or umbilical hernia in the presence of pendulous abdomen or a diffuse venter extensus.

### *Contraindications.*

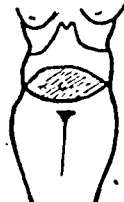
Presumably the risk implied by operative treatment of this affection is comparable to the risk involved in radical operation for any large hernia, including the umbilical; and the

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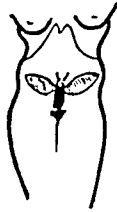
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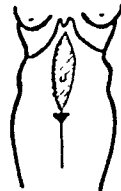
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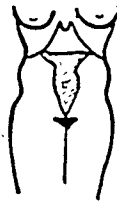
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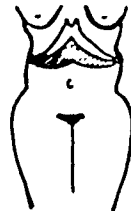
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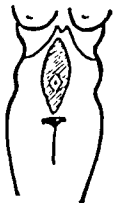
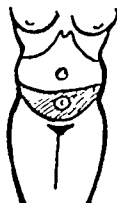
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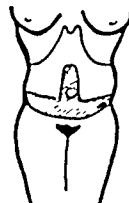
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a. Schenelmann  
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b.



Babcock

Fig. 3.

same contraindications hold true for both lesions: advanced age, cardiovascular disease, chronic bronchitis — as the most frequent contraindications. In addition there are some contraindications of local character. Thus, if intertrigo be present, it should be abolished before the operation. If the patient is known to be disposed to keloid formation, presumably some reservation should be exercised in suggesting operative treatment.

For preoperative prophylaxis it is advisable to get the patient in as good a physical condition as possible, without confinement to bed.

### *Operative Treatment.*

The two most important principles of operative therapy are *thorough asepsis* and *minute hemostasis*. As a matter of fact, the various operative methods suggested are based on the same principle, namely: excision of the superfluous subcutaneous adipose tissue + skin; and chiefly they differ merely in the way of the incision and its localization. Then, of course, the technique will vary according to whether it is decided to leave the umbilicus untouched, perform omphalectomy or transposition of the umbilicus.

The technique employed by us is as follows:

Preoperative outline of the incisions on the skin of the patient in an erect posture. Nitrous oxide—oxygen—ether anesthesia, sometimes introduced with intravenous injection of citodan.

If it be desirable in the first seance to correct the abnormality infraumbilically, the procedure is as follows: Large transverse, downwards convex, incision from one anterior superior iliac spine to the other, through the skin and subcutis, about 3 cm. proximally to Poupart's ligament and the symphysis, corresponding to the growth round at the base of the pendulous abdomen — or slightly proximally hereto. In the midline the downward convex incision lies about one hands breadth distally to the umbilicus. The interval between the two incisions has to be individualized so that the wound can be sutured without tightening.

After the incisions are made, forceps are applied to the skin edges, by means of which the skin is pulled upwards and the

intermediate skin area and subcutis are cut free with long smooth strokes of the knife. Then the skin + subcutis are extirpated, leaving the fascia uncovered from the umbilical transversal to the symphysis. As already mentioned, the following hemostasis has to be particularly thorough, and this is the most time-consuming part of the operation. In view of the large wound surface, as a routine measure, prophylactic powdering with sulfathiazole-penicillin is applied by means of a spray. The operation is concluded by drawing the edges of the wound together with forceps and suturing with silk through the skin and subcutis. This operation can be performed on an average in 30—40 min.

With this technique 25 patients were operated (see Fig. 3).

This technique corresponds mostly to the method first employed by *Jolly* (1911).

*Thorek*, who uses practically the same method, emphasizes a couple of details as particularly important: The two incisions should be convergent in the depths and meet just anteriorly to the fascia so that this is disclosed as little as practicable — in order better to avoid exudate in the operating field and retracted scars. Undoubtedly these arguments are correct in principle. On the other hand, it is tempting — as we have done — to remove as much adipose tissue as justifiable in order to relieve the patient as much as possible.

This technique has been employed for lipectomia parietalis abdominis in 5 other patients, in 3 of whom the pendulous abdomen was complicated by prolapse of the abdominal wall or ventral hernia. In these cases, besides lipectomy, the abdominal wall was sutured transversally, or ventral herniotomy was performed. In the two remaining patients, ventrofixation of the uterus was performed at the same time on account of recurrent uterine prolapse; and in one of these cases also pyramidalis plastic was performed on account of urinary incontinence. With the operating technique here described, the umbilicus is displaced a little downwards, but this will seldom compromise the cosmetic results. The matter stands differently, however, if the umbilicus beforehand has been downwards displaced by traction. If so, its distance from the symphysis after

Jolly's operation will be too short, and this will not look very well. In cases of this kind, therefore, omphalectomy has to be performed or transposition of the umbilicus. In one case we performed lipectomy + omphalectomy after a method that appears to have been given first by Schepelmann in 1918 (see Fig. 3). This method differs from that of Jolly only in the incisions being laid a little higher on the abdomen and the upper incision being upwards convex proximally to the umbilicus.

If the patient insists, that the umbilicus must be preserved, omphalotransposition may be performed. In one case we have done this, employing a procedure corresponding to transposition of the nipple in mastopéxie esthétique ad modum Mornard, with circumscision of the umbilicus and lipectomy ad modum Schepelmann. Before suturing of the skin, a guiding wire is inserted vertically from the umbilicus up through the upper flap and this is pulled downwards. Then the defect after the lipectomy is sutured, and a transverse oval piece of the skin round the guiding wire is excised, a little smaller than the circumference of the umbilicus, which then is delivered through the excision, and its edges sutured to the skin.

In the literature also other methods have been given for transposition of the umbilicus — though all similar in principle (Flesch, Thebesius & Weinsheimer, Schepelmann).

In diffuse venter extensus accompanied by symptoms so severe that the patients also wished an operative correction of the supra-umbilical part of the abdomen, we have operated on 3 patients in 2 seances. In the first seance, lipectomy ad modum Jolly was performed. In the second seance, after a shorter or longer period, corresponding lipectomy was performed through transverse oval incisions between the umbilical transversal and both costal margins.

Several other operative methods have been suggested, but we have no experiences with them.

For operative treatment of diffuse venter extensus Küster has given the following method: Incision in the midline from the epigastrium to the symphysis with circumscision of the umbilicus and — at the proximal and distal ends of this — two transversal incisions. Removal of the skin and a suitable

amount of the adipose layer as far out to the sides as justifiable. Extirpation of the underlying subcutis. Excision of superfluous skin. Closing of the wound, with the umbilicus preserved (see Fig. 3).

In similar cases, Shepelmann employs a longitudinal oval incision from the epigastrium to the symphysis, with or without omphalectomy (see Fig. 3).

As early as 1901 Spaulding published a method aiming in principle to reduce a state of venter propendens by excision of adipose tissue from two longitudinal, paramedian, oval incisions (see Fig. 3). Weinhold employs a so-called clover-leaf incision, consisting of 3 oval incisions from a point just below the umbilicus. One incision runs downwards in the midline, while the remaining two run obliquely upwards and laterally. Finally, mention is to be made of Depage's incision: transversal incision in the epigastrium from the ends of which incisions are made downwards and medially, continuing in a large median, oval incision. Suturing of the wound gives a T-shaped scar. For lipectomy in the supra-umbilical zone Thorek employs his »bat-wing incision« (see Fig. 3).

It is difficult to say anything about the advantages and drawbacks of the methods mentioned. In principle, to us they seem more complicated and hardly more effective than those employed by us.

Postoperatively the patients are treated with compressing bandages. They are allowed to get up on the day after the operation, and they are watched closely with a view to the appearance of a hematoma in the wound.

Half of the sutures are removed after 10 days, the rest after 14 days.

### *Therapeutic Results.*

As far as we have been able to find out, only casuistic reports have been published on the results from lipectomy for pendulous abdomen, and in a greater majority of the cases these results are stated to have been satisfactory.

A survey of our 38 operations on 35 patients shows the results given below. The weight of the removed tissue varies from 600 to 6500 g., averaging a little over 2300 g.

*Postoperative course:* None of the patients dies, and in 31 cases the postoperative course was uncomplicated, with primary healing of the wound. General complications arose in 2 cases: shock in one, multiple pulmonary infarcts in the other. As to local complications, 2 patients presented marginal necrosis of the skin due to excessive tightening of the wound edges, or preservation of two small amounts of subcutaneous adipose tissue. This complication results in slow healing of the wound, and the scar is not as nice as usual.

Further, 2 cases of hematoma formation are to be noted — in both of them the hematoma yielded to puncture and aspiration — besides 1 case of suppuration, which subsided on a minor revision of the wound. It should be realized that such complications may occur, and this is to be kept in mind when the surgeon advises the patient to submit to operative treatment. On the other hand, it is to be emphasized that, with the exception of one case none of the complications has been of serious character.

### *Immediate Results.*

The immediate result from the operative treatment may be estimated on the basis of the state of the patient on the discharge from the hospital, or an observation period of 6 months at the most for all 35 patients.

The result has to be designated as satisfactory in 33 patients. The term "satisfactory" means, that both the patients and the surgeon are satisfied with the outcome, that a sufficient amount of adipose tissue has been removed, and that the wound has healed.

In 2 patients the result has to be characterized as unsatisfactory, as the patient or the surgeon — or both of them — are dissatisfied. In one case the patient was disappointed because the course of the treatment was more protracted than reckoned — owing to suppuration of the wound; objectively, however, the result was otherwise satisfactory. In the other case the wound failed to heal because of skin necrosis; but later on it healed spontaneously.

With such a short observation period, of course, any estimate of the permanent results is out of the question. Only two of

these patients were operated on before 1945. In order to get some idea about the later course of such cases, we have examined 17 patients with an observation period varying from 6 months to 6 years, and averaging nearly 1 year. In 16 of these patients the result has to be characterized as good. The patients were satisfied with the outcome, most of them even very happy that they had got rid of their pendulous abdomen; and all the patients had no longer any complaints.

*Physical examination* revealed no recurrence in any case. The scar was not equally nice in all the cases, but this is something the patient should be told about before the operation. In one case, in which the permanent result has to be characterized as unsatisfactory, the patient had wished the operation performed chiefly for cosmetic reason, and now she was dissatisfied with the outcome — largely because she was a nudist.

Late complications were observed only in two cases — and at that, only of minor consequence — namely: in one case an insignificant keloid formation in the scar; in the other case the medial part of the scar was adherent to the fascia, giving some tightening of the scar up towards the umbilicus.

On recapitulation, the operative treatment for venter propendens, especially pendulous abdomen, may be said to be a measure that is able to relieve or abolish the symptoms of the lesion. In cases where these symptoms are serious, and where conservative treatment is considered futile — or has been tried in vain — operative treatment has to be looked upon as indicated. The risk implied by this form of treatment is relatively slight, when the material is selected properly. As to the permanent result we are not able yet to say anything with certainty, but from our present experiences it looks as if the lesion does not apt to recur.

### *Summary.*

The classifying of venter propendens is briefly outlined, and a brief description is given of its etiology, pathogenesis, clinical features and treatment. The indications and contra-indications for operative treatment are discussed.

An account is given of a material comprising 35 patients who have been treated operatively for pendulous abdomen or for diffuse venter propendens. In 31 cases the postoperative course was completely uneventful, while general complications arose in 2 cases, local complications in 5.

The immediate result has to be characterized as satisfactory in 33 cases, unsatisfactory in 2. In 17 patients with an observation period of from 6 months to 6 years the result has to be designated as good in 16, middling in one.

Recurrence of the affection was not observed in any case.

For properly selected patients the operative treatment is to be recommended on adequate and thoroughly considered indications.

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## EXPOSURE LATITUDE, RANGE OF DEPTH (PERMISSIBLE VARIATION OF DEPTH) AND FIELD OF APPLICABILITY IN ROENTGENOGRAPHY

By  
*Torben Francis, M. D.*

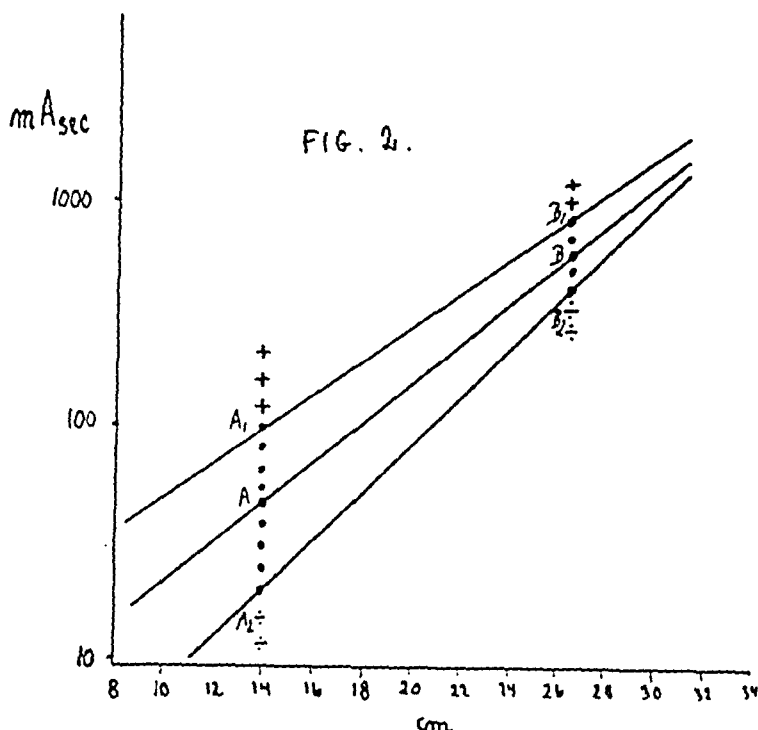
Within the diagnostic radiographic technique the exposure time (in milliamperere seconds) and the voltage (in kilovolts) are in practice based on an estimate of the size of the subject (the part of the patient to be examined). This procedure is universally applied all over the world and is generally sufficient. However, it makes great demands on the experience of the staff and its ability to estimate the subjects correctly, and the method is not sufficiently good for particularly difficult examinations where it is of importance to get the pictures of a definite quality or where supplementary pictures cannot be taken, for instance in cases of very ill patients.

It has, therefore, been attempted to construct principles of exposure based on rational and exact calculations instead of those based merely on estimation of the subject.

Such principles have been constructed by *Jerman, Profillich, Weber & Russo, Franke, Pape & Reiniger, Zakowsky, Huyler, Francis, Hill and Eddy.*

In order to obtain a rational estimate of the subject and be able to calculate from this a suitable voltage and exposure time in each individual case these writers have partly measured the thickness of the subject in centimeters and on this basis calculated voltage and exposure time, and partly constructed photo-electric measuring apparatuses which, under the influence of X-rays sent through the subject, indicate the most expedient exposure time.

Measuring of the subject or the absorption of X-rays constitutes the best possible basis for the calculation of exposure time,



a suitable exposure time for each individual subject from a milliamper-second curve, when the thickness of the subject was measured in centimeters.

Fig. 1 illustrates such an exposure curve for a Siemens X-ray ball working with a fixed voltage of 60 kilovolts and an amperage of 10 milliamperes. The paper is spaced off logarithmically for the ordinate and in centimeters for the abscissa. The thicknesses of the subjects have been recorded in centimeters along the abscissa and the exposure times in milliamper seconds along the ordinate. The curve was constructed on the basis of a number of radiographs, the best of which were noted down and a straight line afterwards drawn through. All other factors were kept constant.

A question which it was particularly desirable to have elucidated was that of exposure latitude and change of latitude under different conditions of taking. In 1944 various investigations into this problem were commenced here in the X-ray department, *Bispebjerg Hospital*.

Logarithmic paper like that described above is applied, where

the subject thicknesses in centimeter are indicated along the abscissa and the exposure times logarithmically in milliamperere seconds along the ordinate. The results are entered of a so-called fork-taking of a certain specified subject, e. g. a hip area with a thickness of 14 cm. Fork exposure consists in the taking of a number of radiographs with a constant voltage but with varying exposure times of the same subject. The times of exposure increase, e. g. the time applied is 20 per cent longer than the preceding time. By this method we obtain a number of radiographs differing in intensity, some being overexposed, while some are underexposed and some are serviceable. The serviceable pictures form the latitude for a radiograph of a subject of that particular thickness taken under the same conditions (Fig. 2).

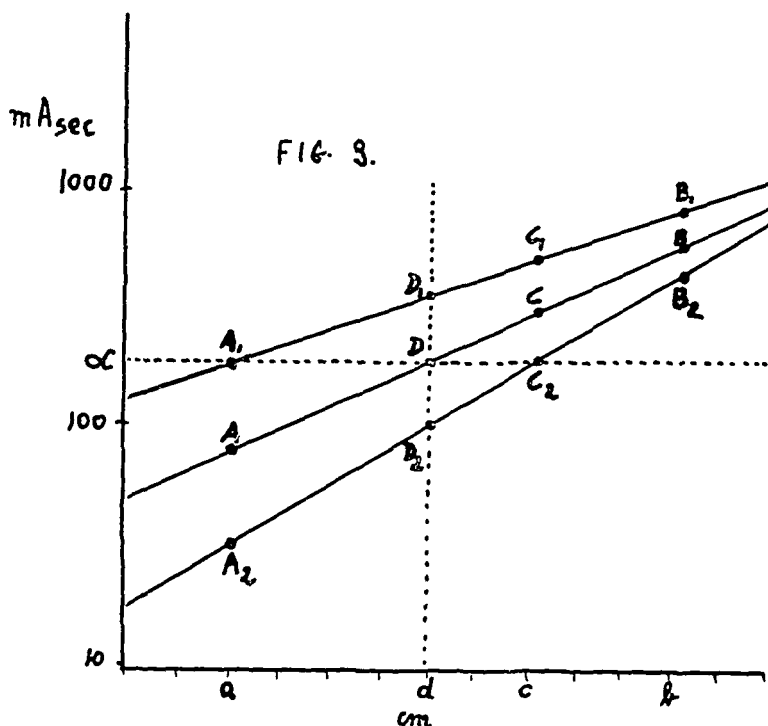
A fork exposure of a thicker subject, e. g. a lateral picture of a lumbar vertebral column 26 cm. thick, is undertaken in exactly the same manner, and the results are recorded in the same manner on the logarithmic paper.

The best one of the serviceable radiographs is chosen for each subject. This will generally prove to lie almost in the middle. A line drawn through these two points (A and B) is a milliamperere-second curve lying in the centre of the latitude. Any taking of a subject the thickness of which has been measured in advance will be quantitatively correct by application of the exposure time indicated by the line  $AB^1$ .

Similarly the limit between the correctly exposed and the overexposed pictures is found by drawing a straight line between points  $A_1$  and  $B_1$ . This line indicates the upper limit to the latitude. A corresponding line drawn through  $A_2$  and  $B_2$  indicates the lower limit to the latitude.

It appears from these curves that, under certain circumstances, the exposure latitude may be rather considerable, and that the exposure latitude is highly dependent on the thickness of the subject, thus increasing considerably at decreasing thickness and reversely decreasing greatly when the thickness increases. When the thickness of the subject has decreased to a certain point and the exposure latitude correspondingly become

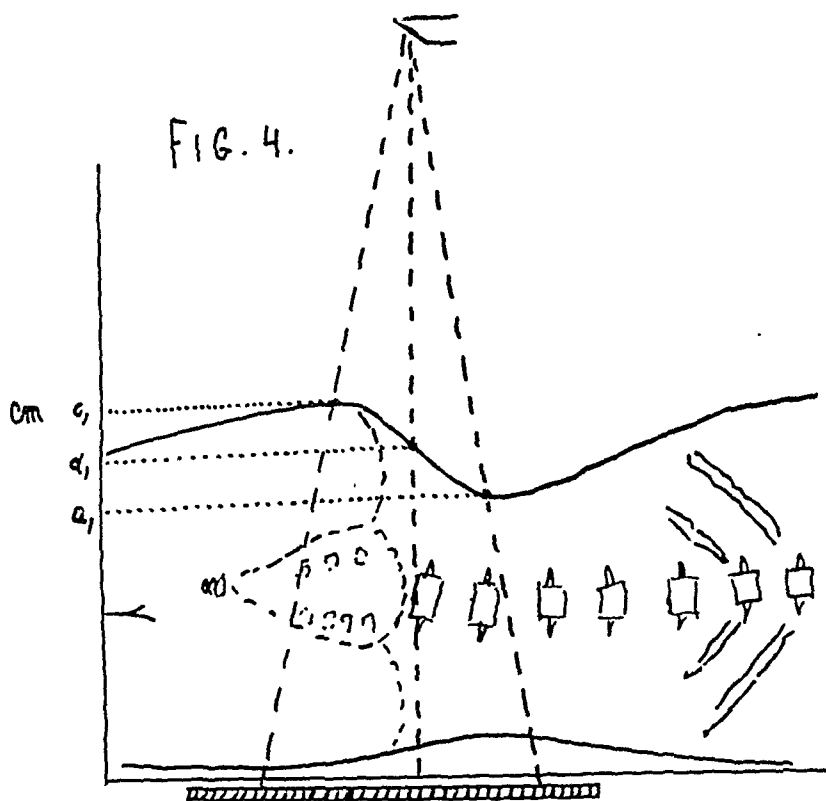
<sup>1)</sup> Conditions are slightly different where subjects with air-containing organs are concerned (see later).



very big there will occur a change in the character of the picture towards a very great contrast. If the thickness is very small, e. g. under 12 cm., the contrast becomes so great that the picture is unserviceable in practice. Reversely the radiograph will become more grey and contrast-less at increasing thickness of the subject and correspondingly diminished latitude. When the thickness exceeds for instance 32 cm. the picture becomes so grey and contrast-less that it is unserviceable.

These facts teach us that a certain, constant "combination" of voltage and other factors of radiography has a limited field of applicability. This field of applicability is indicated in centimeters as the difference between the highest and the lowest permissible thicknesses of the subject, and the limits are found at the thickness where the exposure latitude becomes extremely small or extremely big.

The principle of exposure applied here makes it possible not only to determine latitude and field of applicability, but also to indicate fairly exactly a so-called "range of depth" or "per-



missible variation of depth". By this range is understood the greatest difference of thickness permissible for the subject at the individual taking. This range of depth is indicated in centimeters as the difference between the biggest and the smallest permissible thickness of the subject.

Fig. 3 illustrates the latitude for a certain combination. The definition of point  $A_1$  is the maximum exposure,  $\alpha$  milliamperere seconds, of subject  $a$ . It follows that if the exposure is  $\alpha$  milliamperere seconds and the combination the same,  $a$  is of minimum thickness. Point  $C_2$  indicates in a corresponding manner the minimum exposure,  $\alpha$  milliamperere seconds, of subject  $c$ , from which it follows that if the exposure is  $\alpha$  milliamperere seconds and the combination the same,  $c$  is of maximum thickness.  $c$  minus  $a$  cm. indicates the range of depth or the variation of depth permissible for one and the same combination and an exposure of  $\alpha$  milliamperere seconds.

With an exposure of  $\alpha$  milliamperere seconds a subject of a thickness or diameter of  $d$  cm. is submitted to the quantitatively

most suitable exposure. Subject *c* is exposed to the quantity of X-rays that will just give a serviceable picture, and subject *a* is exposed to the largest quantity of X-rays that can be given without the picture becoming unserviceable. All subjects of a diameter lying between *c* and *a* are exposed to such quantities that the radiographs taken become serviceable.

This means in practice that an irregularly formed subject with different depths — e.g. the hip area in Lorentz' projection, the shoulder area ventrodorsally, or the lumbosacral column in a lateral taking (Fig. 4) — should be exposed in such a manner that the range of depth is not exceeded. Accordingly one of the medium-sized diameters of the subject, e.g.  $d_1$ , should be chosen for determination of the most expedient exposure. The corresponding exposure time,  $a_1$ , should be read from the curve, after which it should be seen that the maximum diameter  $c_1$  and the minimum  $a_1$  of the subject do not fall outside the range of depth. In case these facts are observed the radiograph of this area will be quantitatively serviceable all over. If, on the other hand, the maximum or the minimum diameter, or both, fall outside the range of depth it is impossible, by a single taking, to produce a thoroughly serviceable radiograph of this area. In that case it will be necessary to divide the area concerned in two or more subjects and take radiographs of each separately.

A great number of experimental investigations into latitude, range of depth, and field of applicability under the many different conditions within diagnostic radiography, where the subjects vary infinitely in both shape and size and composition of tissue, have revealed the following facts, which ought to be known by all who work with diagnostic radiography:

- 1) For any combination and taking of a radiograph there is found an exposure latitude the upper and lower limits of which should not be exceeded.

- 2) For one and the same combination the exposure latitude varies with the thickness of the subject, becoming smaller with increasing thickness and bigger with decreasing thickness.

- 3) For any combination and taking of a radiograph there is found a range of depth, or a permissible variation of depth, the size of which increases or decreases inversely proportional to the thickness of the subject, in the same manner as the expo-

sure latitude, and the limits of which are determined by the exposure latitude.

4) For any combination there is found a field of applicability, which can be indicated in centimeters of the subject thickness. The upper limit of this field has been reached when the radiograph becomes grey and contrast-less, which coincides with a very considerable diminution of the exposure latitude. The lower limit has been reached when the contrast becomes too great, which coincides with enormous enlargement of the exposure latitude.

5) The best radiographs are obtained with a moderate exposure latitude and a moderate range of depth in the middle of the field of applicability.

6) These observations apply in principle to any subject irrespective of its structure, also to the air-containing regions (thorax, meteoristic abdomen) with the exception that the thickness of the subject is calculated as the total thickness minus the thickness of the air-containing layers, since absorption by air of X-rays and secondary radiation can be left out of account.

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## THE OCCURRENCE OF EPITHELIOID CELL GRANULOMAS IN HUMAN BONE MARROW

With special reference to the diagnostic value of sternal puncture  
in Boeck's sarcoid and the differential diagnosis of sarcoidosis,  
miliary tuberculosis and brucellosis.

By

*Harald Gormsen, M. D.*

Although examination of *smears* of sternal punctures is used on a large scale as a diagnostic procedure in clinical work, the utilization of *histologic sections* of sternal punctures is scarcely as common as this simple method deserves.

As pointed out in previous papers (12, 13) the examination of histologic sections of sternal punctures must in many cases be considered a necessary supplement to the examination of smears in order to obtain exact hematologic diagnoses e.g. to aid the decision as to whether there is an aplasia, hypoplasia, normal cellularity or hyperplasia of the marrow, to decide whether an abundance of lymphocytes and monocytes in smears is due to an infiltration of the marrow by the cells concerned, to estimate the amount of megacaryocytes in the marrow and the amount of blood pigment in the reticular cells etc. Even outside the purely hematologic field examination of histologic sections of sternal punctures may be of diagnostic value, e.g. for the diagnosis of tumor metastases, lipoidoses, reticuloses, in rare cases lymphogranulomatosis and, further, *Boeck's sarcoid*, *miliary tuberculosis* and *brucellosis*.

In this report an account will be given of the diagnostic value of sternal puncture in *Boeck's sarcoid* and of the difficulties involved in the differentiation of granulomas in this disease from those found in miliary tuberculosis and brucellosis.

It is well-known that the usual histologic picture in *Boeck's sarcoid* consists of a well defined epithelioid cell granuloma with

sparse or completely lacking surrounding lymphocytic infiltration, but with occasional lymphocytes within the granuloma itself between the individual epithelioid cells. Necrosis is absent or minimal in extent, and giant cells, if present at all, are rare.

The granulomas of *Boeck's sarcoid* are widely distributed and may very frequently be demonstrated. Thus, *van Beek & Haex* (1) and *Buchem* (3) demonstrated the granulomas in 13 out of 18 diagnosis is therefore most commonly verified by biopsy of lymph nodes and tonsils. By liver biopsy too the granulomas may very frequently be demonstrated. Thus, *van Beek & Haex* (1) and *Buchem* (3) demonstrated the granulomas in 13 out of 18 patients.

The granulomas occur very frequently in the bone marrow also and curiously enough — unlike other focal changes in the bone marrow — they are found predominantly in the yellow fatty marrow. Within the latter they show a predilection for the peripheral bones of the extremities, a fact which is utilized to a great extent for diagnostic roentgenography of hands and feet (*"ostitis multiplex cystoides Jüngling"* (18)).

Among 734 cases of *Boeck's sarcoid* gathered from the literature *Gravesen* (16) found bone changes in 256 instances. In only 2 of these 256 cases were the bone changes noted in locations other than hands and feet alone; 15 cases showed alterations in other bones as well as in hands and feet. In all other cases changes were found *only* in the hands and feet. In *Gravesen's* own material comprising 112 cases, 32 showed roentgenological bone changes, of which 4 were present only in locations other than the hands and feet (1 in the ulna, 1 in the tibia and 2 in the ossa nasalia).

Most frequently the granulomas occur in the bones of the outermost and the middle phalanges of fingers and toes. They are less frequent in the metacarpal bones and in the first phalanges, and less frequent still in metatarsal bones. Lesions have seldom been observed in the ossa nasalia or in the carpal, tarsal, or long bones. Several bones are often affected at the same time; frequently both hands and both feet are the seat of lesions.

In several cases where X-ray examinations of the whole skeleton have been performed in patients suffering from *Boeck's sarcoid*, it has not been possible to find anything — except in hands

and feet — which could with certainty be considered osseous *Boeck's* sarcoid. *Lindegaard Nielsen* (21) and *Gottlieb* (15) have published cases with supposed lesions in the costa, os naviculare and columna, respectively.

The above statements are based almost exclusively on roentgenological observations. Owing to the good prognosis of the disease only few autopsy examinations of the skeleton have been made. In all, only between 50 and 60 cases with autopsy appear to be reported in the literature. These include about 10 cases (2, 8, 11, 13, 16, 17, 22, 27, 31) in addition to the 44 collected by *Rubin & Pinner* (28). In only comparatively few autopsied cases has the bone marrow been examined. In these cases there was found a wide distribution of granulomas in the bone marrow of the vertebrae, costae, femur, and long bones of the arm. These changes were in addition to those found in the bones of the hands and feet. It is therefore to be supposed that the bone marrow is the seat of granulomas in *Boeck's* sarcoid to a far greater extent than is indicated by roentgenological observations. *Schumann* (29) has stressed the fact that the granulomas seldom destroy the bone tissue except in bones of the hands and feet. This probably accounts for the fact that only few cases show roentgenologically demonstrable lesions in locations other than hands and feet.

Autopsy examinations of the sternum in patients with *Boeck's* sarcoid do not appear to be available.

Apparently, examinations of *sternal punctures* in patients with *Boeck's* sarcoid have been made on only a rather small scale. *Leitner* (20) (9 patients) *Gravesen* (16) (2 patients) and *Weber & Lauber* (34) (1 patient) have all searched in vain for granulomas in sections of sternal punctures.

Typical granulomas have been noted in histologic sections of sternal punctures by the following investigators: *Dressler* (6) (1 case), *Ehlertsen* (7) (1 case), *Esser* (9) (1 case), *Gormsen* (14) (5 cases of 11 with a total of 16 punctures), *Lindegaard Nielsen* (21) (1 case of 2), *B. Nielsen* (24) (3 cases of 12) and *Stahel* (32) (1 case).

Demonstration of epithelioid cell granulomas in sections of sternal punctures from patients with *miliary tuberculosis* has previously been reported by *Stahel* (32) (1 case) and by *Schleicher*

(30) (8 cases). *Leitner & Conradin* (19) and *Debré & co-workers* (5) have cultured tubercle bacilli from sternal punctures from patients with miliary tuberculosis. The demonstration of miliary tuberculosis through sternal puncture by both histologic and bacteriologic means is not astonishing considering the diffuse dissemination of the pathology in this disease.

*Wohlwill* (36) seems to have been the first to describe the occurrence of epithelioid cell granulomas in the bone marrow in brucellosis in man; further case reports, all with autopsy examination, were described by *Wegener* (35) and *Rabson* (25). More recently, *Sundberg & Spink* (33) have reported the results of examinations of sternal punctures in 9 patients with brucellosis. In 4 of the patients epithelioid cell granulomas were shown in histologic sections; in 2 of the patients *brucella abortus* Bang was cultured from the sternal puncture.

#### *Own Investigations.*

*Technic:* In addition to smears, 2 or 3 hematoxylineosin-stained histologic sections (in some cases also v. Gieson-stained sections) of sternal punctures have been examined in all cases. The maximum aspiration volume is about  $\frac{1}{2}$  c.c. of marrow; most frequently it is considerably less. After preparation of smears from a few drops, the remainder of the puncture material is squirted into a small tube, where it is left to coagulate. After the clot has been carefully loosened, a fixing fluid (formalin water or Helly's fluid) is poured over it. The tissue is then imbedded in paraffin prior to sectioning. — In all cases in which granulomas were found, investigations of Ziehl-Neelsen-stained sections were also made.

It is, of course, of decisive importance that the puncture contains a fairly abundant number of marrow particles.

*Material:* Sternal punctures from 39 patients with *Boeck's sarcoid*, 5 patients with miliary tuberculosis and 22 patients with brucellosis.

*Boeck's sarcoid:* In 30 of the 39 cases the diagnosis was histologically verified by tonsillar or lymph node biopsy, in 9 cases the diagnosis was extremely probable (characteristic X-ray findings in lungs, hands or feet, negative or very weakly positive tuberculin reaction, skin manifestations, in a few cases uveoparotitis

syndrome, in a great number of cases positive Kveim reaction and histologic verification of the latter). 35 other cases of suspected Boeck's sarcoid were studied, but have been omitted from this series because the above positive findings were absent, and a hilar adenitis was generally the only suggestive sign of sarcoidosis. In none of these 35 cases granulomas were found in the sternal punctures.

Granulomas were found in sections of 6 of the 30 sternal punctures from patients with histologically verified Boeck's sarcoid. In the non-verified group granulomas were found in 4 cases of 9.

In all, granulomas were thus demonstrated in the sections of sternal punctures from 10 of 39 patients, i.e. in about 25 per cent.

In only 2 cases were epithelioid cells found in smears of sternal punctures, in both cases in patients with verified Boeck's sarcoid. A granuloma was demonstrated in the histologic section of one of these cases, but not in the other.

*Miliary tuberculosis:* 3 cases which were originally thought to be Boeck's sarcoid, but later proved to be miliary tuberculosis with protracted course were erroneously diagnosed as Boeck's sarcoid because the granulomas appeared without necrosis and without tubercle bacilli. In 2 other cases the diagnosis of miliary tuberculosis was made on the basis of bacillary findings in granulomas, one of which showed necrosis (fig. 8).

*Brucellosis:* In one case the diagnosis of Boeck's sarcoid was made on a typical epithelioid cell granuloma encircled by a great number of lymphocytes and eosinophilic leucocytes. The patient from whom the puncture was obtained showed a weak seroreaction to brucellosis at a later examination, whereas symptoms of sarcoidosis were lacking.

After becoming acquainted with the report by Sundberg & Spink (33) on the occurrence of epithelioid cell granulomas in the bone marrow in patients with brucellosis, I examined sternal punctures from 22 patients with serologically verified brucellosis. No less than 15 of the 22 patients had granulomas in the bone marrow. (A detailed report of the histologic and bacteriologic findings in sternal punctures from patients with brucellosis will appear in a later work in collaboration with Martin Kristensen).

With regard to the *histologic characteristics* of the granulomas in the 3 diseases the following statements may be made:

1) *Boeck's sarcoid* (10 cases): The granulomas varied very much in appearance and in size, as appears from figs. 1—4.

In 3 of the 10 cases more than one granuloma was found in the histologic section (maximum 4 granulomas — fig. 1). In 5 of the 10 cases a thin rim of lymphocytes and comparatively many eosinophilic leucocytes were noted round the granuloma; in 3 cases no encircling cell rim was found (figs. 2 and 4) and in 2 cases a broad rim of lymphocytes was present with considerable numbers of eosinophilic leucocytes in the periphery of the lymphocyte rim (figs 1 and 3). In 4 cases lymphocytes were seen between the epithelioid cells (fig. 3). 2 cases showed giant cells of the Langhans type (figs. 2 and 4), and in 1 case sparse necrosis was found (fig. 1).

2) *Miliary tuberculosis* (5 cases): These granulomas, too, varied considerably (figs. 5—9). In 3 cases more than 1 granuloma was found in the section. In 3 cases a thin rim of lymphocytes and a great many eosinophilic leucocytes were found round the granulomas (figs. 5, 8, and 9). In 2 of these 3 cases furthermore a great number of plasma cells and neutrophilic leucocytes were observed. In 1 case no surrounding cell rim was found (fig. 7), only in 1 case a broad lymphocyte rim was present (fig. 6), in the peripheral parts of which many eosinophilic leucocytes were seen. In 2 cases lymphocytes were noted between the epithelioid cells (fig. 6). In only 2 cases were Langhans' giant cells (fig. 9) found, and in one of these foreign-body giant cells (fig. 9) were also present. Necrosis was found in only 1 case (fig. 8); tubercle bacilli, in 2 cases only.

3) *Brucellosis* (15 cases): The granulomas were generally smaller and less distinctly limited than those in Boeck's sarcoid and miliary tuberculosis, and the epithelioid cells were often smaller than in the 2 other diseases (figs. 10—12). In all 15 cases several (2—6) granulomas were found in the section. In 9 of the cases there were found round the granulomas a great number of lymphocytes, eosinophilic and neutrophilic leucocytes and, further, a great number of plasma cells. In 2 cases the eosinophilic leucocytes were especially numerous. A broad rim of lymphocytes was not found in any case. No necrosis was seen in any case. Giant cells were found in only 2 cases. They were

of the Langhans' type in one (fig. 11), and of foreign-body type in the other (fig. 12).

In histologic sections of about 3000 sternal punctures from patients with many widely different diseases including many and various infectious conditions I have found epithelioid cell granulomas in only one case in addition to the 3 above-mentioned diseases. This case was that of a woman (57 years old) who was supposed to be suffering from metastases from a mammary carcinoma. The puncture from this patient showed 4 adjacent epithelioid cell granulomas encircled by broad rims of lymphocytes. In this patient the diagnosis of neither Boeck's sarcoid, miliary tuberculosis or brucellosis could be established.

In a series of sections of red bone marrow from the upper part of the femoral cavity and from the sternum from an incidental autopsy material comprising 300 patients with widely different diseases, among which were many infections (not including tuberculosis), an epithelioid cell granuloma was found in only one case, namely in a 62-year-old man with cancer ventriculi, without signs of either fresh or old tuberculosis nor sarcoidosis. This granuloma was found in the femoral marrow.

Incidental findings of epithelioid cell granulomas in the bone marrow in cases other than miliary tuberculosis, Boeck's sarcoid and brucellosis must thus be considered extremely rare.

In sections of sternal marrow from 20 autopsied cases of pulmonary tuberculosis without signs of miliary tuberculosis, typical caseating tubercles with bacilli were found in 8 cases, apparently originating from a terminal dissemination of the tuberculosis.

On the other hand, I have in no case found tubercles in sections of sternal punctures from 31 patients with various forms of non-terminal tuberculosis, mostly pulmonary in type.

### *Discussion.*

In the material reported epithelioid cell granulomas were demonstrated in histologic sections of sternal punctures in 10 of 39 patients with Boeck's sarcoid (i.e. in about 25 per cent), in 5 of 5 patients with miliary tuberculosis and in 15 of 22 patients with brucellosis.

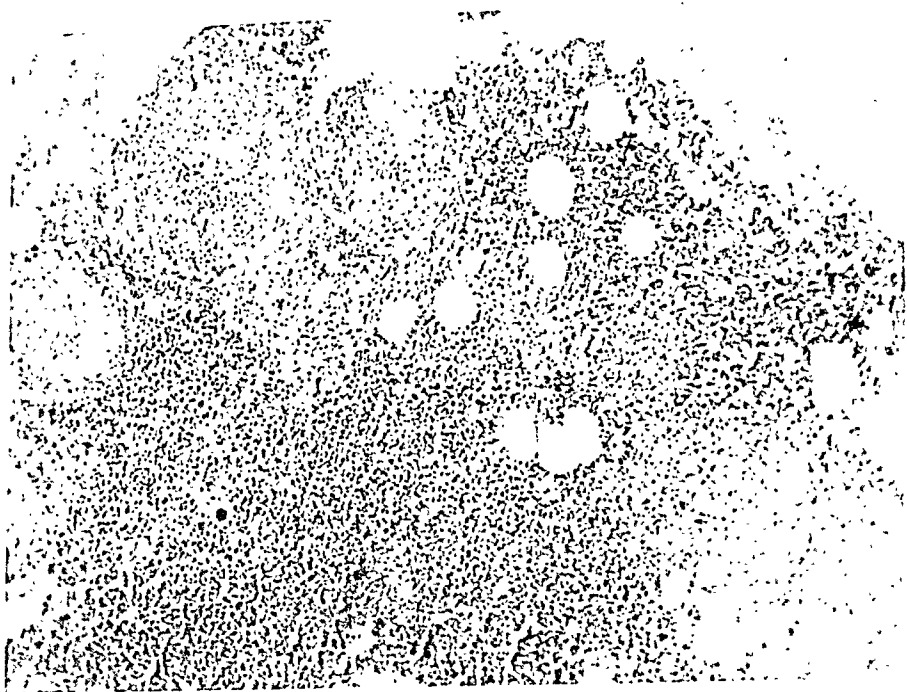


Fig. 1. Section of marrow showing Boeck granulomas. ( $\times 100$ ).

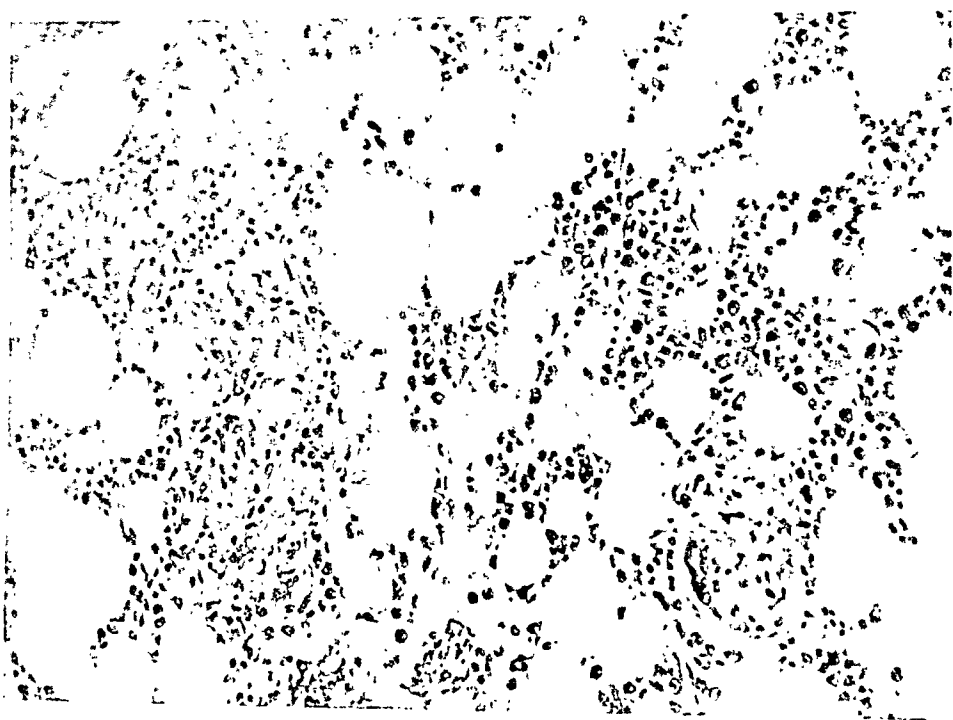


Fig. 2. Section of marrow showing Boeck granulomas. ( $\times 400$ ).



Fig. 3. Section of marrow showing Boeck granuloma. ( $\times 210$ ).

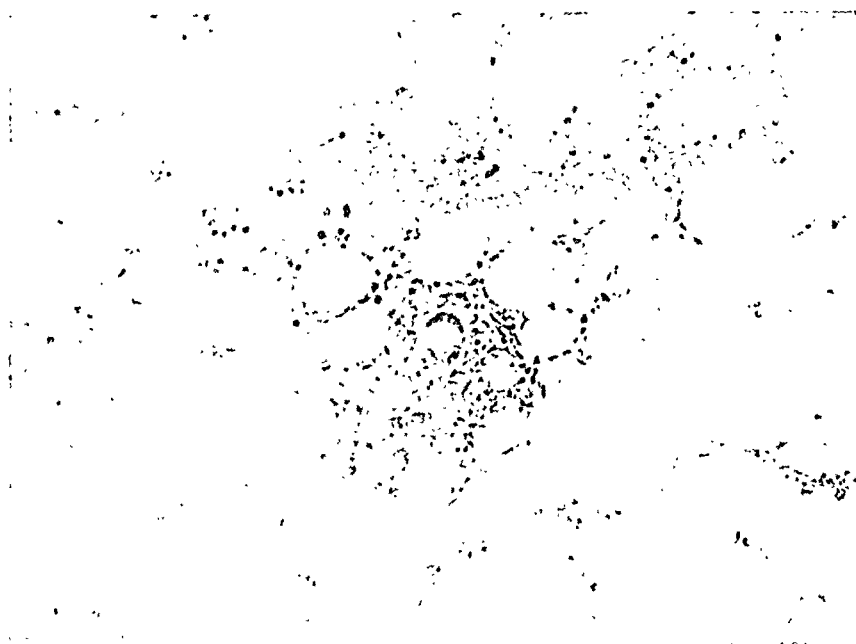


Fig. 4. Section of marrow showing Boeck granuloma. ( $\times 210$ ).

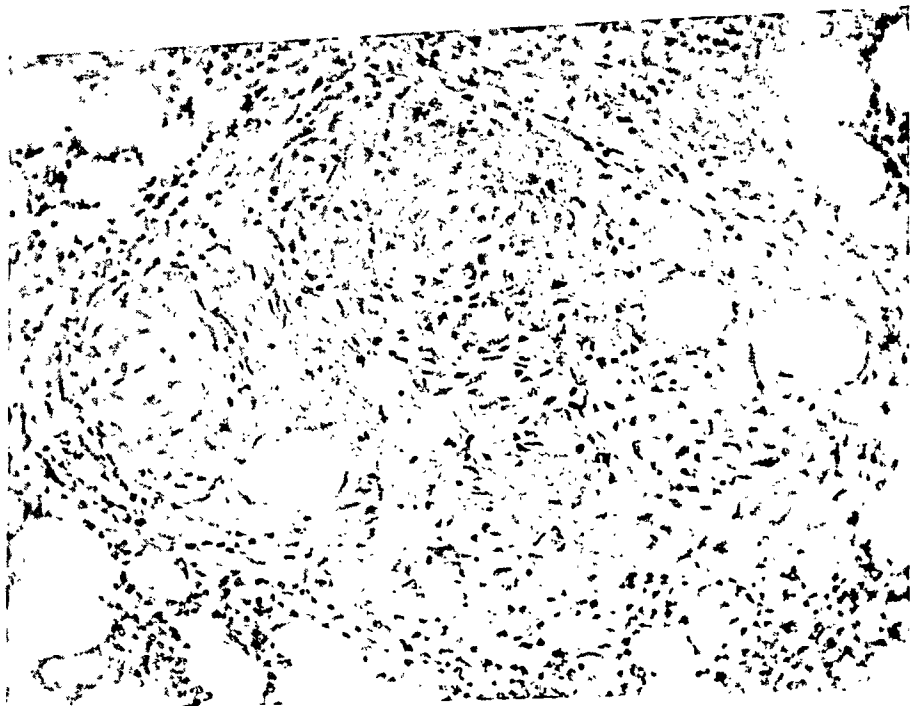


Fig.-5. Section of marrow showing miliary tubercle. ( $\times 210$ ).

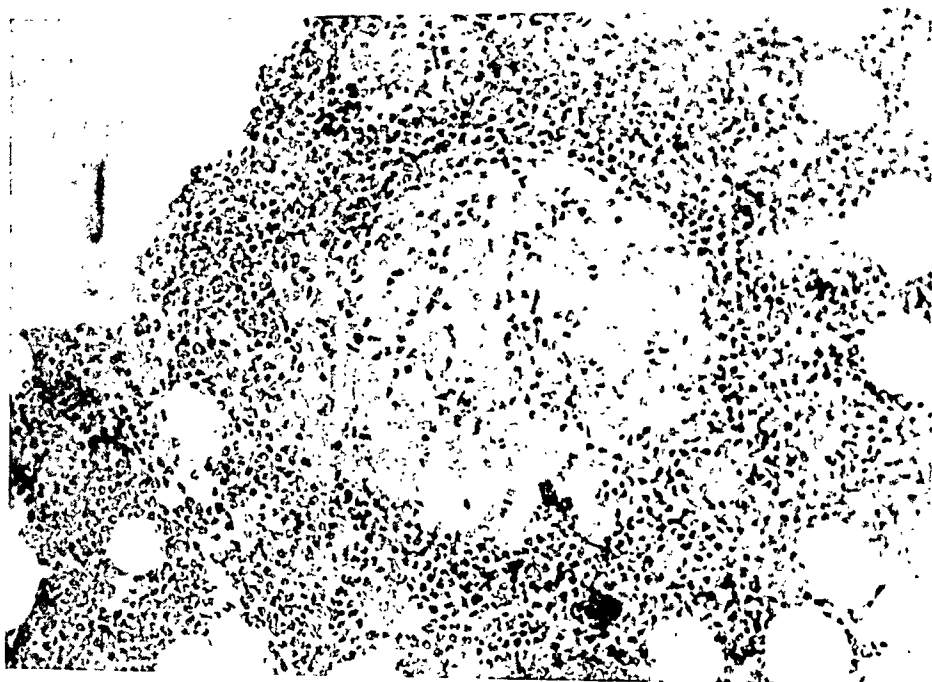


Fig. 6. Section of marrow showing miliary tubercle. ( $\times 210$ ).

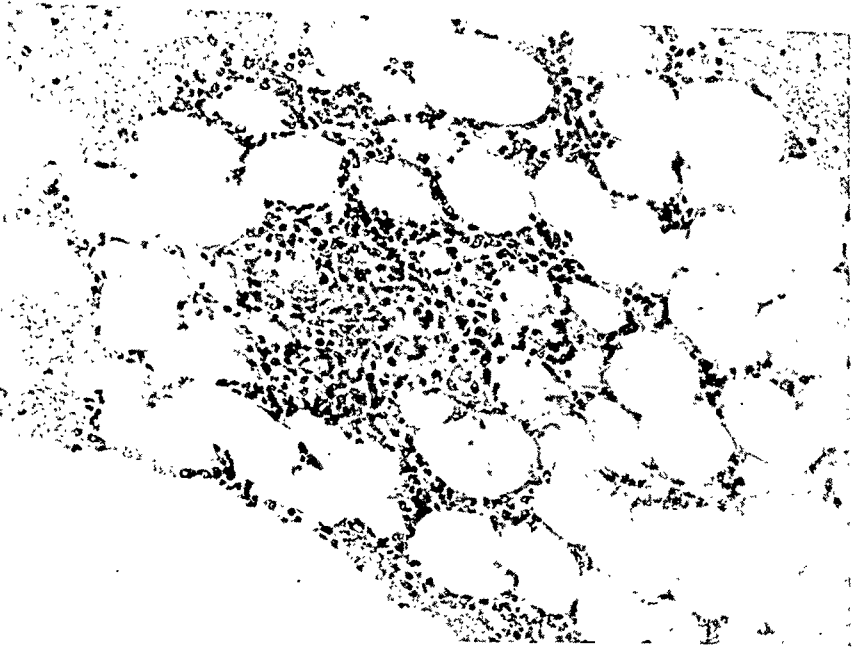


Fig. 7. Section of marrow showing miliary tubercle. ( $\times 210$ ).

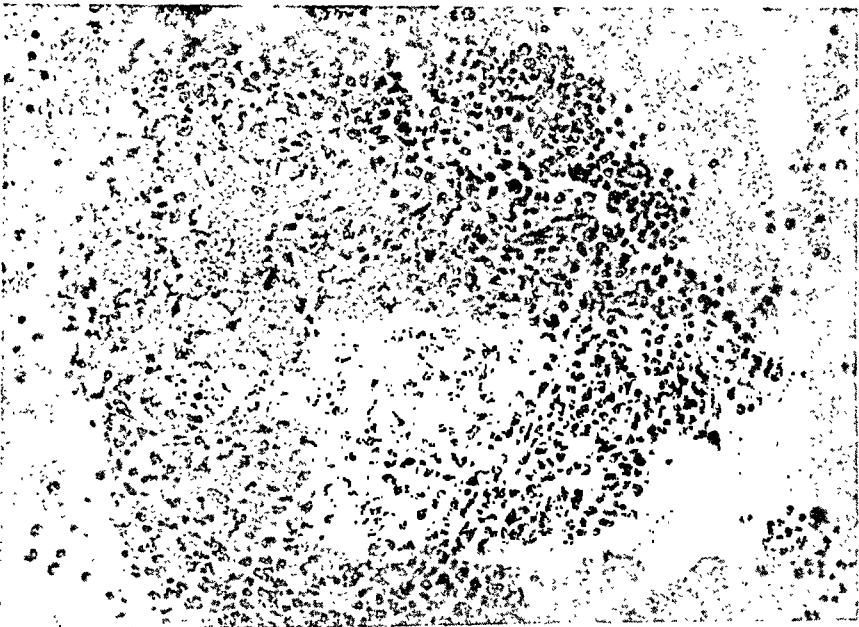


Fig. 8. Section of marrow showing caseating miliary tubercle.  
( $\times 210$ ).

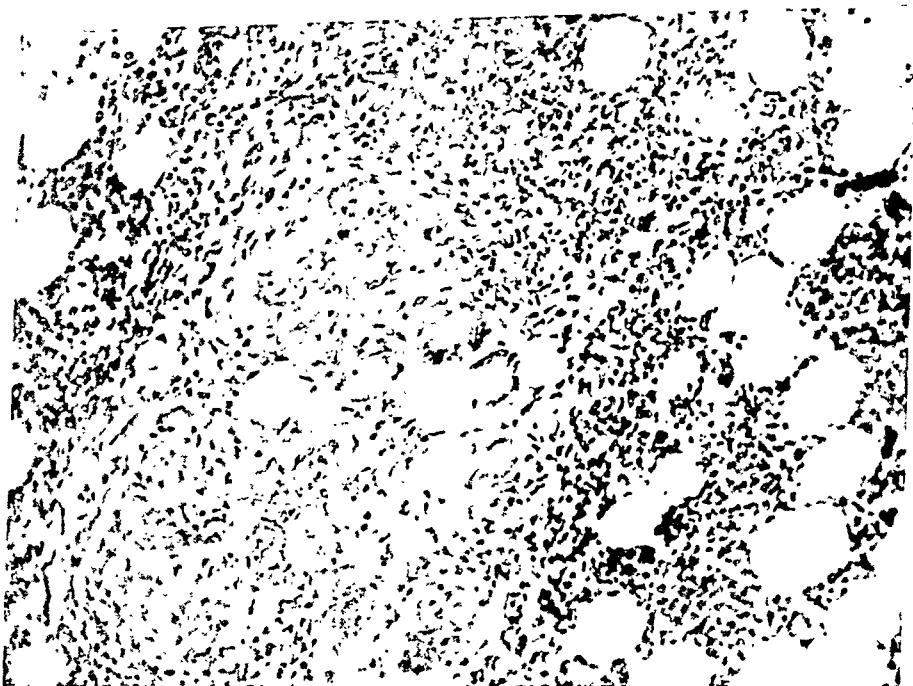


Fig. 9. Section of marrow showing miliary tubercle with giant cells of Langhans and foreign body type. ( $\times 210$ ).

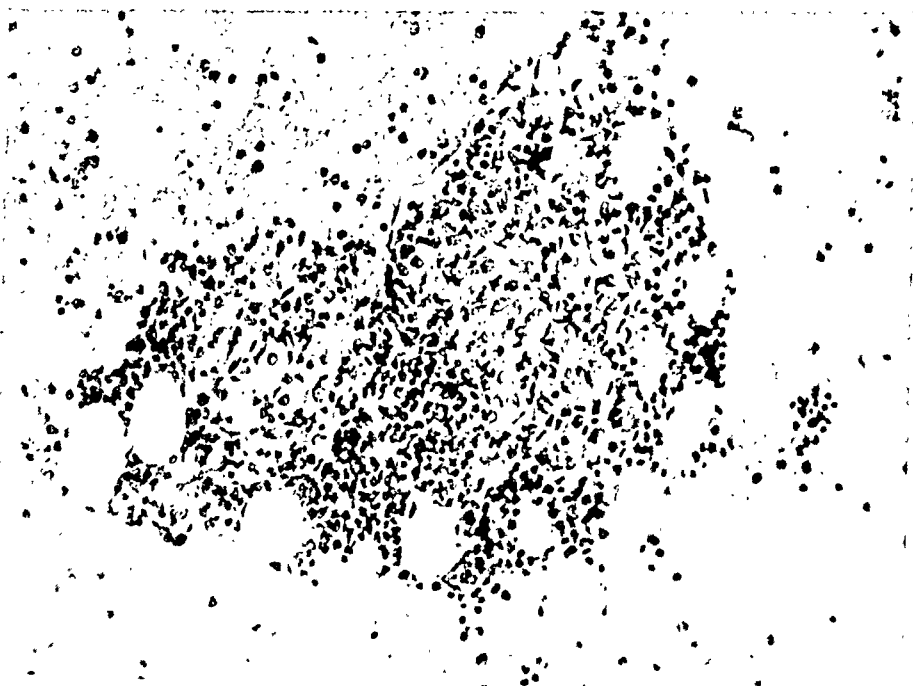


Fig. 10. Section of marrow showing brucellosis granulomas. ( $\times 210$ ).

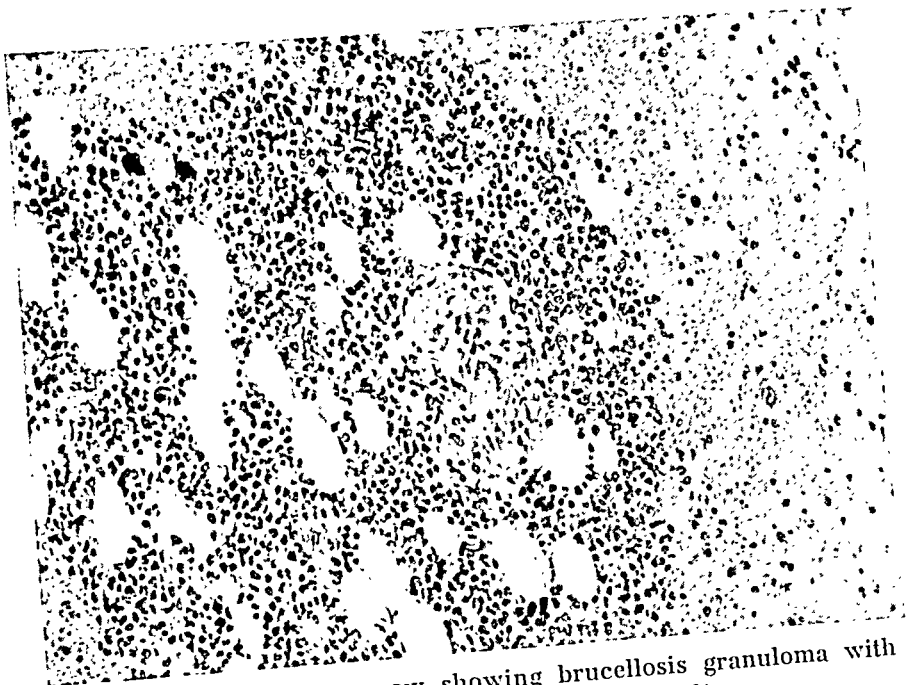


Fig. 11. Section of marrow showing brucellosis granuloma with giant cell of Langhans type. ( $\times 210$ ).

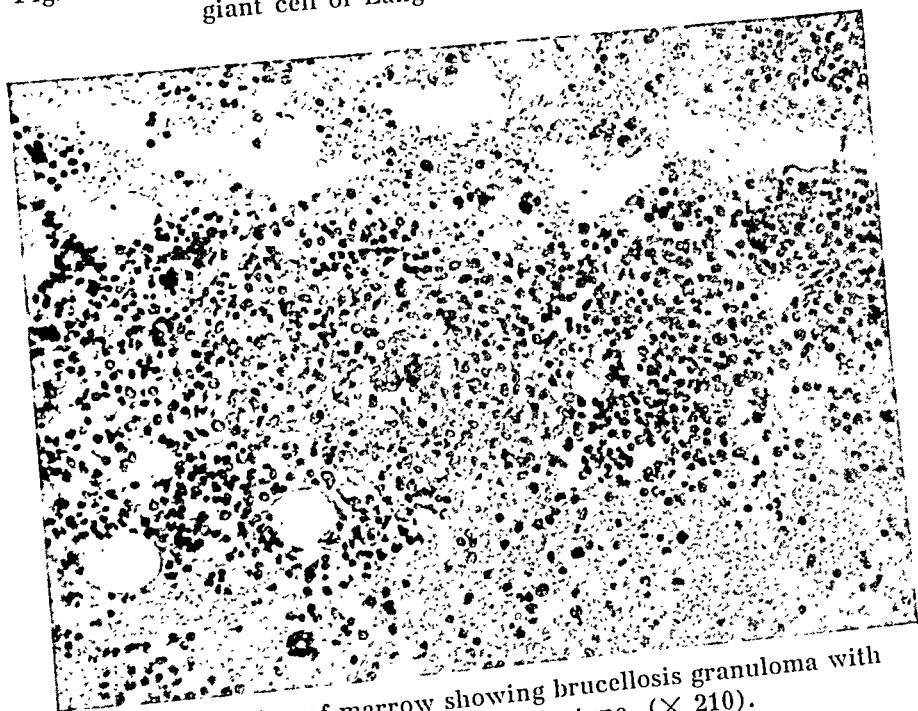


Fig. 12. Section of marrow showing brucellosis granuloma with giant cell of foreign body type. ( $\times 210$ ).

Three of the cases of miliary tuberculosis were originally diagnosed erroneously as Boeck's sarcoid because the granulomas were without necrosis and without bacillary findings; in 2 cases the diagnosis of miliary tuberculosis was based on bacillary findings.

One case with granuloma was erroneously diagnosed as Boeck's sarcoid in a patient later found to have brucellosis.

On the basis of the material reported herein it must be said frankly that, if there is neither bacillary finding nor pronounced caseous necrosis in the granulomas, it must be considered impossible to differentiate miliary tuberculosis from Boeck's sarcoid.

The differential diagnostic difficulties posed by the histologic changes in miliary tuberculosis and Boeck's sarcoid have been discussed by *Stahel* (32), *Nickerson* (23) and *Rakov & Taylor* (26).

*Stahel* (32) has pointed out that sometimes miliary tuberculosis shows only a thin surrounding rim of lymphocytes and that there may be eosinophilia in the periphery of the nodule. Further, that the reaction around the sarcoid-granulomas is still slighter than that in miliary tuberculosis.

*Nickerson* (23), in 5 examined cases of sarcoidosis in the bone marrow has found each lesion surrounded by a dense rim of lymphocytes and eosinophils. In one of the cases, which was interpreted as an acute fulminating one, sparse areas of necrosis were noted. In the other cases no necrosis was seen. *Nickerson* claims that the giant cells here are different from those seen in tuberculosis; they show moderate variation in size, are usually much larger, and contain many more nuclei which are evenly distributed throughout the cell and are seldom arranged in the elliptical manner typical of tuberculosis giant cells.

*Rakov & Taylor* (26) stress the fact that it is exceedingly difficult to differentiate sarcoidosis from truly noncaseating tuberculosis. These authors emphasize the larger size and more cuboidal shape of the epithelioid cells in the individual sarcoid and point out that the individual sarcoids do not fuse to produce a conglomerate sarcoid in the manner that primary tubercles produce the conglomerate tubercle.

As can be seen, if comparisons are made between the micro-

photos nos. 2 and 5, 3 and 6, and 4 and 7, representing granulomas from cases of Boeck's sarcoid and miliary tuberculosis, respectively, in the absence of bacillary findings and pronounced caseous necrosis, it is impossible on the basis of the granuloma alone to make the diagnosis of one of these 2 diseases and to differentiate it positively from the other.

All the histologic characteristics of the sarcoid-granulomas mentioned at the beginning of the paper (i.e. absence of lymphocytes round the granulomas, lymphocytes between the epithelioid cells, lack of giant cells and necrosis) have been demonstrated in several of the cases of miliary tuberculosis. On the other hand, broad encircling rims of lymphocytes and typical Langhans' giant cells have been found in the sarcoid granulomas in several cases. In a single case of sarcoid slight necrosis was noted. The cell proliferation round the granulomas is of no guidance. Eosinophils have in several cases been noted round the miliary tubercles.

The difficulties in the differential diagnosis of granulomas in brucellosis, Boeck's sarcoid, and miliary tuberculosis, respectively, have been discussed by *Sundberg & Spink* (33), who stress the fact that the distinction is particularly difficult between sarcoidosis and brucellosis. In the latter disease, they point out that caseous necrosis is absent, both Langhans' and foreign body giant cells may be present, and the lesions are often surrounded peripherally by small numbers of degenerating marrow cells, neutrophils, eosinophils, and plasma cells.

In my material it seems that granulomas due to brucellosis most often have a rather characteristic appearance which to some extent differs from the granulomas in Boeck's sarcoid and miliary tuberculosis. The granulomas in brucellosis are, generally, considerably smaller and less distinctly limited than the granulomas in Boeck's sarcoid and miliary tuberculosis. The epithelioid cells are most often less rich in protoplasm, and the granulomas seldom show giant cells, never necroses or broad surrounding rims of lymphocytes, but, on the other hand, they have rims of lymphocytes, many eosinophilic leucocytes and more or less plasma cells and neutrophilic leucocytes. — But if figs. 2, 4 and 11 are compared, it is seen that in certain cases

it may be impossible to differentiate the brucellosis-granulomas from those in Boeck's sarcoid and miliary tuberculosis.

Whereas it thus seems to be impossible to differentiate Boeck's sarcoid with certainty from miliary tuberculosis on the histologic findings in the bone marrow — unless there are bacillary findings or pronounced caseous necrosis — the granulomas in brucellosis, once the investigator is familiar with the appearance of the granulomas, will seldom cause differential diagnostic difficulties towards Boeck's sarcoid and miliary tuberculosis.

### *Conclusions.*

It seems impossible with certainty to differentiate Boeck's sarcoid from miliary tuberculosis on the basis of the histologic appearance of the granulomas found in the bone marrow, unless there are bacillary findings or pronounced caseous necrosis. In certain cases it may be impossible to differentiate the bone marrow granulomas in brucellosis from the granulomas in sarcoidosis and miliary tuberculosis, but most frequently it is possible to differentiate these granulomas from those of the 2 other diseases.

### *Summary.*

In histologic sections of sternal punctures epithelioid cell granulomas have been found in 10 of 39 patients with Boeck's sarcoid (i. e. in about 25 per cent), in 5 of 5 patients with miliary tuberculosis and in 15 of 22 patients with brucellosis.

The differential diagnostic difficulties connected with distinguishing the granulomas from each of these 3 diseases are discussed, and it is pointed out that it must be considered impossible to differentiate sarcoid-granulomas from non-caseating tubercles. In certain cases it will be impossible to differentiate brucellosis-granulomas from sarcoid-granulomas and tubercles. In most cases, however, brucellosis-granulomas are rather different from the granulomas in the other 2 diseases.

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## A CASE OF PURPURA HAEMORRHAGICA AFTER ADMINISTRATION OF QUININE WITH SPECIFIC THROM- BOCYTOLYSIS DEMONSTRATED IN VITRO

By  
*L. C. Grandjean.*

A patient suffering from purpura haemorrhagica, which proved to have been brought about by quinine, was admitted to the Bispebjerg Hospital.

The patient, a woman aged 25, had 3 months previously been a patient in an epidemic hospital under a diagnosis of influenza. While in the epidemic hospital she had an attack of haemoptysis. She was therefore referred to a tuberculosis hospital (the Øresundshospital), to which she was admitted after a stay in a neurologic department on account of infiltrations in the head, sequelae of sinusitis, and influenza. During her stay in this department her right antrum of Highmore was X-rayed, and there was found a lateral density, which might correspond to a mucous membrane swelling, but otherwise nothing abnormal except infiltrations and peritendinitis. After treatment by massage, and with lucosil and allypropynal the patient was admitted to a tuberculosis department on account of haemoptysis of unknown cause. In the course of the first few days she coughed up 200 ml. of bloody expectoration. Except for a positive Mantoux-reaction after injection of one-tenth mg. tuberculin there were no signs indicative of a tuberculous disease. The measuring of blood pressure was observed, however, to effect pronounced petechiae. As, in addition, the patient indicated that menses had been profuse the past 6 months or so, it was decided — 8 days after her admission — to examine the time of bleeding, which proved to be 3 minutes, the time of coagulating, 2½ minutes, and the number of blood platelets.

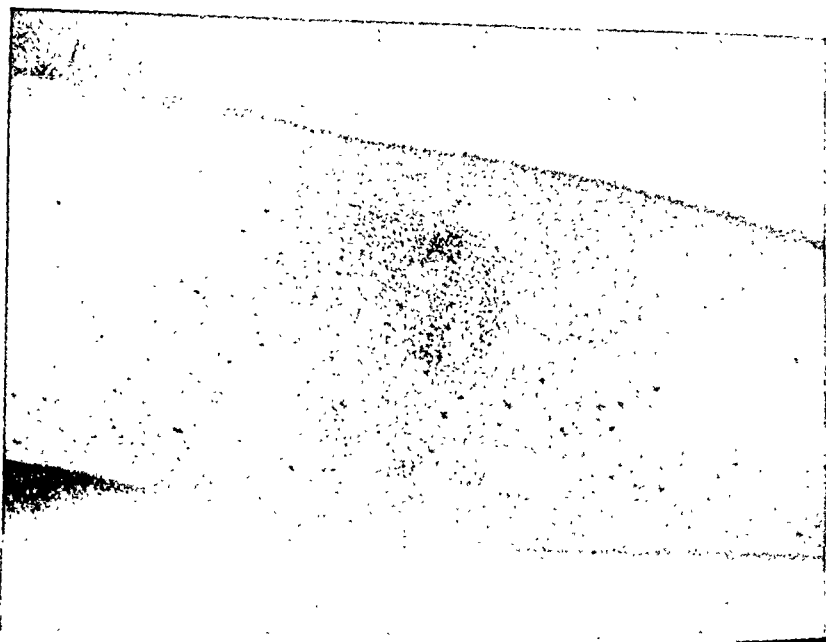


Fig. 1. Back-side of antibrachium shortly after superficial pinching of the integument. Note the big haematoma with surrounding petechias.

which amounted to 660,000. The remaining blood examination likewise showed normal conditions.

5 days after her discharge from the Øresundshospital the patient was admitted to the Bispebjerg Hospital on account of haematemesis and attacks of fever.

She complained of tiredness of about 2 months' duration, and occasional rises in temperature to 39–40° C.

She had had several attacks of haematemesis. In connection with these attacks she had observed pin-head-sized spots, resembling pinching marks, scattered all over the body. On the eve of admission the patient again had an attack of haematemesis and rise in temperature to 39° C. This attack was associated with pain radiating from the right iliac fossa to the epigastrium and further to the left flank. The pain was relieved by injections of morphia. On the day of admission there occurred several petechias and blood-filled bullae on the skin.

On admission: The patient made an anaemic impression. Capillary haemorrhages were seen scattered on the skin, chiefly

on face, back and chest. At the right axilla there was observed a number of small haemorrhages corresponding to pressure from the shoulder-strap of her underwear.

There was bleeding from the gums as well as from the lower lip. Finally there was the typical sanguineous fetor from the mouth. The temperature was normal on entry and remained so during her entire stay.

A diagnosis was made of purpura haemorrhagica.

The day after admission the time of bleeding was measured according to Duke's method and found to be  $> 10$  minutes. A slight, superficial nip at the skin on the forearm gave rise to a quickly growing haematoma, which the next day had assumed a dark-blue colour and covered almost the entire inner side of the forearm (Fig. 1).

A complete blood examination made 3 days after her admission revealed slight anaemia of a hypochromic nature, and a blood platelet number of 70,000. On Göthlin's capillary resistance test there were found 10 petechias. In the course of the next 7 days the time of bleeding decreased, the number of platelets rose, and the haematomas brought about by pinching grew smaller. Examination on the 8th day showed normal conditions.

By questioning the patient as to her use of medicaments before the occurrence of the disease we were informed that she had often taken tablets against headache. Her own doctor told us that he had prescribed tbl. phenemal mites, tbl. gelonida, and tbl. saridone over a fairly long period. Special attention was given to the latter preparation as a possible cause of the purpura, because until April 1946 saridone contained among its constituents 6 cg. sedormid. In addition, the patient had in 1944 been given quinine for induction of labour, without, however, presenting any tendency to haemorrhage. She had not taken quinine since, as far as she knew.

She remembered, however, that she had taken 2 pills immediately before her last attack. 2 hours later she got a shivering fit followed by haemorrhages.

We succeeded in procuring the remaining pills, which proved on analysis to be quinine pills containing ab. 8 cg. quinine sulphate each.

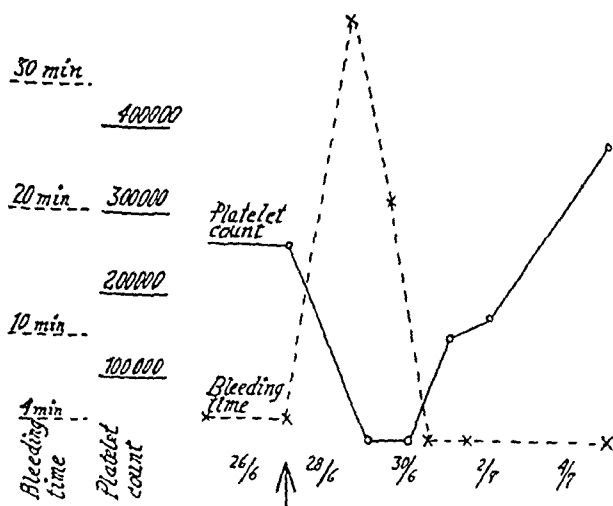


Fig. 2. Abscissa: Time in days.  
At the arrow administration of 8 cg quinine sulphate.

In order to ascertain whether the quinine pills might have been the provoking factor the patient was given one of the procured pills containing 8 cg. quinine sulphate — after platelet count, capillary resistance test, and bleeding time had showed normal conditions.

10 minutes later the patient felt unwell with headache, which increased in intensity. By mistake the patient had, however, been orientated in advance of the experiment.

After 2 hours there occurred a number of blood-filled bullae scattered over face and body.

3 or 4 hours later the blue spot on the lower lip as well as the gingival haemorrhages present on admission were reproduced. In addition the patient developed abdominal pain and tenderness of the crural and the femoral muscles.

Fig. 2 illustrates the curves plotted for platelet count and bleeding time within the following days.

Through this experiment we seemed to have established the fact that the purpura on account of which the patient was admitted had been brought about by tablets containing 8 cg. quinine sulphate each.

It appears from literature that both quinine, quinine sulphate, quinine hydrochloride, and quinine tannate may bring about

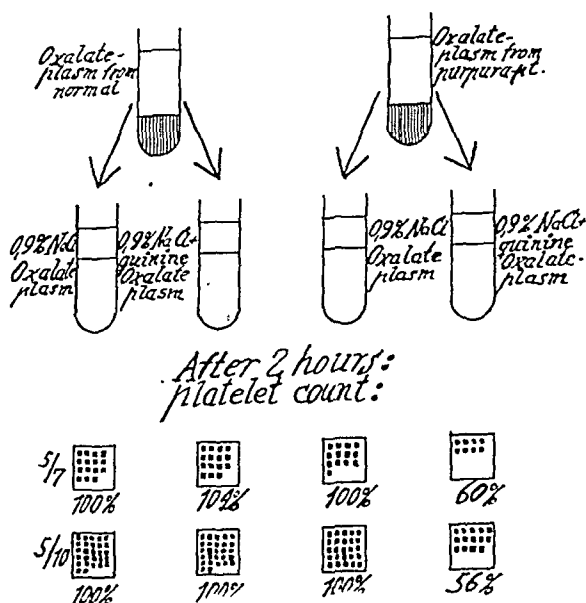


Fig. 3. Schematic representation of the *in vitro* experiment. The number of platelets in plasma without addition of quinine is indicated as 100 %. One dot in the squares represents 10,000 platelets.

allergic purpura. Common to all the cases mentioned in literature is a shorter or longer symptom-free period, during which the patient has not taken in the substance, after which renewed intake of the quinine compound, often in smaller doses, provokes severe signs and symptoms.

Common to the above compounds is the quinine group, the stereo-isomer of which, the quinidine, is said to cause neither purpura nor any other allergic phenomena.

Since the signs and symptoms came on very shortly after the administration of quinine, the question suggested itself of an acute change in the circulating blood platelets due to contact with quinine. An *in vitro* experiment was made to ascertain whether this might be the case.

Venous blood was taken from a control subject and from our patient, and oxalate was added to the blood in the usual manner.

2 samples of plasma were pipetted off from each glass. To two of the samples we added one-fifth volume of physiological salt-water, and to the two others one-fifth volume of physiological salt-water in which was dissolved quinine sulphate to

saturation. After careful shaking all 4 glasses were left at room temperature for 2 hours. Next the platelets were counted in Zeiss' counting chamber.

The result appears from the above squares (Fig. 3), where each dot represents 10,000 platelets.

3 months later the patient was summoned for a follow-up examination. She had recovered completely. The *in vitro* experiment was repeated, and the result appears from the table (Fig. 3).

Thus, there seems to occur a thrombocytolysis when quinine comes into contact with the blood platelets of this quinine-susceptible patient.

In such cases administration of the purpuriferous quinine compound should be interrupted immediately. As part of the prophylaxis the patient's attention should be called to the quinine-containing »tonic water«, which, according to information from an analysis laboratory, may contain up to 6.8 cg. quinine sulphate in one litre.

#### *Summary.*

A case of hemorrhagic purpura provoked by quinine is reported. A test dosis of 8 cg. quinine sulphate was given to the patient at once provoking an attack of hemorrhagic purpura. Two *in vitro* experiments showed that the platelets of this quinine-susceptible patient by admixture of quinine showed marked thrombocytolysis, while those of normal persons did not.

## THE VITAMIN B COMPLEX; ITS IMPORTANCE AND THERAPEUTIC VALUE IN INTERNAL MEDICINE

By

*Erik Gripwall, M. D.*

During the last few decades no other substances have probably, to the same degree as the vitamins, been subjected to scientific and general interest. This is particularly true as regards the vitamins of the B complex, which will be discussed in the following. Above all, I intend to deal with those substances which are definitely significant in human nutrition, namely, vitamin B<sub>1</sub> or thiamine, vitamin B<sub>2</sub> or riboflavin, and nicotinic acid or the P-P factor. The rest, vitamin B<sub>6</sub> or pyridoxine, and pantothenic acid with no significance in human nutrition, will only be mentioned briefly. All the vitamins of the B complex are soluble in water and occur extensively and closely associated in nature, their fields of action largely overlapping. Through the intense research of the last few decades their chemical structure has been determined, and the synthesis of these substances was thus rendered possible, for the benefit of therapy.

In order to understand the clinical manifestations of vitamin B deficiency, so-called avitaminosis and subvitaminosis, respectively, it seems important to emphasize at once the fact that the above mentioned natural occurrence of these substances in close association, renders the deficiency symptoms complex, with consequent variations in the clinical picture. Before dealing with the special diseases caused by lack of the different factors of the B complex, I will endeavour to outline the conditions under which a vitamin B deficiency may develop in the organism.

- 1) Food lacking in vitamin B. The poor population lives chiefly on carbohydrate, whereby the need for vitamin B<sub>1</sub> is increa-

- sed. The absence of teeth renders mastication difficult and may entail a reduced supply. Certain diets, e. g. in diabetes and gastrointestinal diseases, are deficient in vitamin B.
- 2) Faulty absorption. This is the case in many diseases of the digestive canal, achylia, persistent vomiting and diarrhea.
  - 3) Increased need for vitamin B occurs in infections, particularly with long-standing fever, and in thyreotoxicosis, during pregnancy and lactation.
  - 4) Faulty utilization of vitamin B, e. g. in liver diseases, when the ability of the body to store and utilize the vitamins is disturbed.

The alcoholic diseases are particularly interesting in this connection. Alcohol consumption increases the need for vitamin B<sub>1</sub>. Also, the effect of alcohol on the gastric mucosa interferes with absorption, and faulty utilization may result from a disturbed liver function. It is therefore not surprising that symptoms of B-hypovitaminosis are extremely common in chronic alcoholism.

I will now give an account of the history and treatment of the vitamin B complex. First, a few words about the general properties of vitamin B<sub>1</sub>, or thiamine. It was isolated from rice husks already in 1926 by Janssen and Donath, but was not introduced in therapy until in 1937, when Williams and co-workers determined its structure. As the toxic doses lie considerably higher, indeed 1000 times higher, than the therapeutic, symptoms of poisoning are practically non-existent. It is easily absorbed perorally with a normal gastro-intestinal tract, as well as parenterally, and is stored in the organism, most abundantly in the brain, the liver, the kidneys and the heart. Thiamine is partly destroyed within the organism in relation to the size of metabolism, and about 10 % of the intake is excreted with the urine. In B<sub>1</sub> deficiency, thiamine is excreted fairly rapidly during the first week, after that more slowly; about 20 % of the thiamine deposited is retained obstinately by the tissues also in severe B<sub>1</sub> deficiency. The daily requirement for optimal nutrition may be estimated at 1—2 mg. The need increases with a higher metabolic rate, particularly during hard work. A high carbohydrate intake also increases the need,

whereas fat has a thiamine-sparing action. This accounts for the fact that  $B_1$  deficiency occurs particularly among those peoples who live on an unvaried diet, such as polished rice, poor in vitamin  $B_1$  but rich in carbohydrate.

In regard to the function of vitamin  $B_1$  within the organism, it may now be considered an established fact that, in the capacity of an enzyme, it plays a fundamental part in the intermediary metabolism of carbohydrate. It combines with phosphoric acid and constitutes an enzyme, cocarboxylase, which is concerned with the oxidation of e.g. pyruvic acid which accumulates in blood and tissues in severe  $B_1$  deficiency. In this connection, Peter's and his co-workers' investigations are particularly interesting. They show that tissues poor in vitamin  $B_1$ , the central nervous system in particular, lack the capacity of absorbing oxygen in a normal degree. I will revert to this question later.

We know that severe vitamin  $B_1$  deficiency leads to the classical disease named beriberi, existing in the Orient since the 9th century. The clinical picture is built up by disturbances, partly from the central nervous system, consisting of a symmetric peripheral ascending neuritis, chiefly localized in the legs, partly from the circulatory system with symptoms of severe insufficiency of the heart. The so-called beriberi heart, which has been closely studied by American investigators, presents the classical picture of cardiac decompensation, often with distinct enlargement to the right and, as a very important diagnostic symptom, reduced circulation time. Administration of digitalis and common cardiac stimulants fails to relieve the insufficiency of the circulation, which is also an important diagnostic memorandum, whereas the response to the administration of vitamin  $B_1$  is prompt and often dramatic.

The more severe forms of  $B_1$  deficiency are extremely rare in this country and in other civilized countries. A few cases of beriberi heart, however, are described by Nylin, Rilton and Bjuggren, among others. These cases were alcoholics and patients with severe intestinal disturbances. As far as we are concerned, the milder type of vitamin  $B_1$  deficiency, the so-called hypovitaminosis, is much more interesting. It is often difficult to diagnose, as the clinical picture is not a characteristic

one. In addition, our chemical and physiologic methods of examination for determining the vitamin supply of the organism are too difficult to be carried out routinely in practice or in hospital laboratories. Nevertheless, by careful inquiry as to the diet, we are often able to judge the vitamin standard, something which is frequently neglected in the recording of the case history. At the medical department of Södertälje Hospital we have, during the past years of crisis, had our attention directed to such subclinical states of vitamin B deficiency and have been able to recognize several cases of this kind. In particular, we were concerned with individuals who had lived on an insufficient diet rich in carbohydrate and poor in protein and fat. The symptom picture may be characterized by the following symptoms with many variations: fatigue, general disability, irritability, possibly loss of weight. Common symptoms are: diffuse digestive disorders, such as flatulence, poor appetite, abdominal pains of a vague type and possibly pains and paresthesia in the legs. In the American literature, Lepore and Golder, 1941, have described similar findings. The symptoms subside promptly on administration of the vitamin B complex.

Other diseases which may be considered due to B<sub>1</sub> deficiency and thus are open to B<sub>1</sub> therapy, are alcoholic polyneuritis, neuritis in gravidototoxicosis and diabetes. In delirium tremens and in the so-called Wernicke's syndrome, a disease of the central nervous system in alcoholics, B<sub>1</sub> therapy is of great value.

According to my own experience, vitamin B is useful as a general stimulant in anorexia and in several psychasthenic states, particularly after infections of long duration or disturbances in the digestive canal. It is often astonishing to see how rapidly these patients recover. Personally, I have found that it is important to administer sufficient doses of vitamin B. 20–40 mg of B<sub>1</sub> as well as the whole B complex should be given, preferably intravenously, during a couple of weeks, and after that the dosage should be reduced according to the individual states.

As seen from the foregoing, B<sub>1</sub> therapy is an extremely valuable addition to our therapeutic arsenal, providing the application is properly indicated. On the other hand, the belief that vitamin injections are a universal remedy in pretty well any

disease, is a fallacy which brings discredit on the physician concerned. In this connection I also wish to emphasize that B<sub>1</sub> therapy is not absolutely free from risks. Sundelin has recently reported one case and quoted a number of cases from the American literature, where, after thiamine injections, the patient got an anaphylactic shock, often dramatic enough and in some cases leading to death.

I will now deal with the vitamins of the B<sub>2</sub> complex, in the first place riboflavin. Riboflavin is of fundamental importance in metabolism, in the capacity of a hydrogen-carrier. It is a constituent of the so-called yellow oxidation enzyme, containing phosphoric acid and protein. It is also called lactoflavin, on account of its intense yellow colour. Riboflavin occurs abundantly in several of our common food stuffs, particularly, however, in milk, eggs and liver. The daily human requirement is estimated at 1.5–3 mg. In deficiency states it is retained in the organism more obstinately than thiamine, whereby the danger of avitaminosis is reduced.

Ariboflavinosis occurs partly as a polyvalent deficiency disease, partly as an isolated, markedly monovalent, avitaminosis. The etiology of the uncomplicated ariboflavinosis was not made clear until in 1938, when Sebrell and Butler published their investigations on experimental Riboflavin deficiency in humans. Changes occur after a period of 2–4 months and consist of rhagades formation in the corners of the mouth, possibly change of colour of the lips which become abnormally red and shiny, and of a skin affection resembling seborrhea, around the nose, in the nasolabial folds and on the ears. Lesions of the tongue have also been described. The tongue becomes smooth and markedly reddened with fissures and loss of substance. Dysphagia and koilonychia have also been observed.

In this connection it should be pointed out that several of the above-described epithelial changes, in the mucous membrane may also occur in other well-known pathologic conditions, such as sideropenia, an iron-deficiency disease, and in pellagra. These common features may perhaps indicate a relationship of some kind or other, between the diseases — a reasonable presumption based on the functions of iron and riboflavin in the tissue oxidation.

It would perhaps be of interest to mention that the same changes may be relieved by mitamin B<sub>6</sub>, 20—50 mg daily. Thus, there seems to be no doubt but that the so-called cheilitis may have a varied etiology.

Sydenstricker and co-workers, 1940, reported that certain patients with ariboflavinosis also presented characteristic changes in the eyes, a feeling of lightness in the eyes, lacrimation, photophobia and failing vision due to a plexus of vessels on the surface of the cornea. The changes were sometimes associated with mydriasis and pigmented spots on the iris. The changes subside rapidly and heal, usually, within a few weeks after the administration of 5—15 mg of riboflavin daily. I have myself observed a case of typical ariboflavinosis, which developed after a lengthy treatment, parenterally, with vitamin B<sub>1</sub>. It has also been reported that symptoms of ariboflavinosis have been produced by means of prolonged treatment with nicotinic acid. The administration of the entire B complex in optimal correlation seems therefore to be a rational treatment also in cases of apparently monovalent avitaminosis.

Nicotinic acid or nicotinic acid amide, or niacin, as the Americans name it, is another important factor in the vitamin B complex. Lack of nicotinic acid causes pellagra. This disease occurs endemically in North Italy, the Balkan states and in the south sections of the USA as a result of a deficient and unvaried diet. During the latter part of the 18th century and the beginning of the 19th century, it became widely spread in South Europe.

Pellagrins, however, may also present secondary symptoms, such as disturbed absorption in chronic affections of the intestines, e. g. sprue, and in chronic alcoholism. In 1937 Elvehjelm and his associates were able to identify nicotinic acid amide, and in the following year Fout and co-workers established its efficacy in curing pellagra. The daily human requirement may be estimated at 15—20 mg. Nicotinic acid is a constituent in the structure of two ferments, coenzyme I and II, which like riboflavin, are fundamentally involved in the processes of cell oxidation. Nicotinic acid is about 100 times less toxic than nicotine and has no action on the autonomic nervous system.

As distinguished from nicotinic acid amide, nicotinic acid causes, particularly on parenteral application, a peripheral vasodilatation in the face and on the hands, attended by often intensely smarting and burning sensations in the skin, which last for about 15—20 minutes.

The classical picture of pellagra presents symptoms from 3 organ systems, namely, the skin, the gastro-intestinal tract and the central nervous system. The changes in the skin are well-defined, symmetric and localized chiefly in the parts of the body exposed to light. The skin firstly becomes reddened, then dark-pigmented, swollen and ulcerated. The most prominent symptoms from the digestive canal are stomatitis, gingivitis, enteritis and alchylia in 50 %. The lesions on the tongue are particularly distinct with intense redness, swelling and in some cases a tendency to ulceration. The symptoms from the central nervous system are headache, mental depression, irritability and in severe cases pronounced states of confusion and dementia. A form of encephalitis described by Joliffe and co-workers, in pellagrins and alcoholics, characterized by unconsciousness, convulsions and certain eye symptoms, responded satisfactorily to large doses of nicotinic acid, 200 mg daily, intravenously.

The treatment of pellagra consists of nicotinic acid or amide administered in doses totalling about 500 mg daily. In gastro-intestinal disorders the dosage is 50—100 mg, parenterally. The effect is prompt and, indeed, dramatic. Already within 24 hours there is a noticeable regression of the changes in the skin and the mucosa, as well as of the psychic changes. In regard to the latter, the effect is so striking as to serve as evidence of pellagra as the etiologic factor. Many cases of pellagra are rendered complicated by the lack of  $B_1$ , riboflavin or  $B_6$ . For this reason the entire B complex should be administered simultaneously with nicotinic acid.

Nicotinic acid has also been used in a number of other diseases; in atypical psychosis, stomatitis, gingivitis of uncertain origin, dermatosis after sulfa preparations, in porphyrinuria, etc. No definite therapeutic results may be said to have been achieved. For my own part, I have sometimes noted good results in aphthous stomatitis from daily doses of 50—100 mg. The

vasodilatory effect of nicotinic acid has been utilized in a number of functional and organic vascular affections, such as Raynaud's disease, acrocyanosis and Ménière's disease. The results vary — in Ménière's disease they are sometimes very satisfactory.

Apart from the above described vitamins, the vitamin B group includes a great number of substances. Although their importance in human nutrition has not been fully established, they have been extensively used in therapy. Among them are B<sub>6</sub> or pyridoxine, pantothenic acid, biotin, choline, para-aminobenzoic acid and folic acid. In this connection only pyridoxine and pantothenic acid will be described briefly. B<sub>6</sub> deficiency in rats causes a characteristic dermatitis, the so-called rat pellagra, in dogs and swine a microcytic hypochromic anemia. No specific symptoms of B<sub>6</sub> deficiency in humans have been recognized. Certain investigators hold that patients with Parkinson's disease excrete an insignificant amount of B<sub>6</sub> on administration of the vitamin. Administration of B<sub>6</sub>, however, does not seem to effect the picture, nor have any encouraging results been achieved from therapeutic trials with vitamin B<sub>6</sub> in other diseases of the central nervous system, such as amyotrophic lateral sclerosis and disseminated sclerosis. It has been established that certain cases of cheilitis have been treated successfully with B<sub>6</sub>. No definite relief in diseases of the blood has been achieved.

Pantothenic acid is also synthesized in a crystalline form, and lack of this factor in the food produces dermatitis in chicks. Particularly interesting are certain changes in the adrenal cortex, manifested in hemorrhagic necrosis. Pantothenic acid may also under certain circumstances act as an "anti-gray-hair factor". Black rats kept on a pantothenic acid-deficient diet developed extensive graying of the fur parallel with above described changes in the adrenal cortex. No distinct clinical picture in humans suffering from pantothenic acid deficiency is yet known. An interesting fact is that pantothenic acid has been found to act on certain forms of neuritis, where the other vitamin B components have failed to do so. Certain cases of glossitis and cheilitis are likewise said to have responded satisfactorily.

I will now deal briefly with the question of choice of preparations and mode of application. It is of the greatest importance that only perfectly satisfactory preparations be used. If no manifest, or only mild, deficiency symptoms are present, the peroral therapy will probably be adequate. The following preparations should be noted as perfectly satisfactory, containing all the vitamins of the B complex: Beviton and Bevitotal (Astra), Becozym (Roche) and Beveran. On the basis of my own experiences from many years of observation, I would consider Beviton an extremely effective preparation. It consists of a highly concentrated yeast preparation fortified with extra thiamine; it also contains Ca-K, Na- and Mg-salts + strychnine. For the treatment of more pronounced deficiency symptoms injectable preparations should be chosen, such as Bevitotal or Becozym, 2 ml daily, possibly fortified with those components which dominate the morbid picture. From an economic point of view, Bevitotal will be the cheaper preparation, as it is supplied in capsules of 50 ml.

Finally, some general aspects on the combat of deficiency diseases. In this respect, the prophylactic treatment is of the greatest importance. A well-balanced diet should be devised, which is varied and rich in the vitamins essential to the vital functions of the organism. This is the best possible way of preventing diseases caused by vitamin deficiency.

## CHRONIC LYMPHATIC LEUKAEMIA, ASSOCIATED WITH PERNICIOUS ANAEMIA

Report of a case.

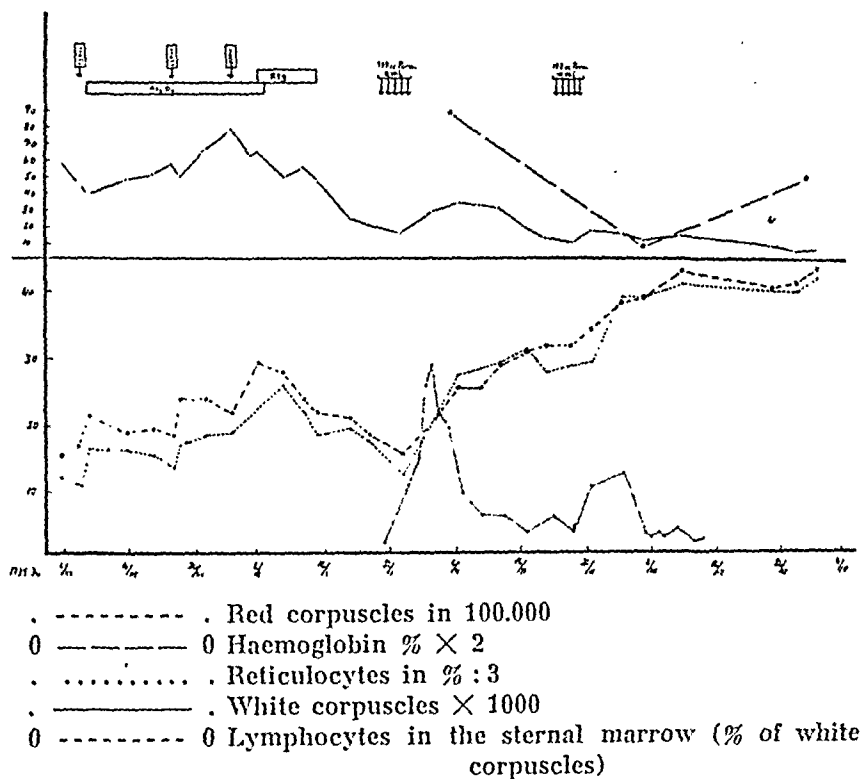
By

*Olav Hanssen.*

Pernicious anaemia as a rule is a primary disease. Sometimes, however, it occurs in persons who already suffer from other disorders. Its association with exophthalmic goitre, chronic arthritis, diabetes, myxoedema, ventricular carcinoma and other diseases, which often are accompanied by chronic gastritis with achylia, is well known.

Iron deficiency anaemia may also sometimes be associated with pernicious anaemia, but the coexistence of pernicious anaemia with other diseases of the blood, especially leukaemia, is rare. The leukanaemia, which Leube described in 1902, was a condition which was characterized by changes in the blood picture similar to those of pernicious anaemia and leukaemia. All now agree, that the condition described by Leube, is not a disease entity, but includes atypical cases of either pernicious anaemia or myelocytic leukaemia. In his textbook Hans Schulten stresses the occasional similarity between chronic lymphatic leukaemia and pernicious anaemia, and says: "In cases with high lymphocyte count one often finds high colour-index, and types of cells, which could not be differentiated from the megalocytes of pernicious anaemia. In several such cases, the investigator thought there might be a combination of lymphatic leukaemia and pernicious anaemia. This is definitely not correct. This diagnosis is only justified if one finds megaloblastic changes in the bone marrow, and a clear-cut response to liver-treatment. Usually one does not have these findings, or one has not searched for them".

According to Maxwell M. Wintrobe (1946) only five acceptable



**Lungs:** Dullness on percussion over the right dorsal base with diminished breath sounds and reduced vocal fremitus. The X-ray diagnosis was: Hilar adenitis. Pleural adhesions on the right side. Infiltration of the lungs (of leucaemic origin?)

**Heart:** Nothing abnormal.

**Liver:** Enlarged, with dullness from 6th costa to 2 cm. below the costal margin.

**Spleen:** Enlarged, and palpable 3-4 cm. below costal margin.

**Abdomen:** Surrounding the umbilicus, mostly above and on the right side, one felt some hard, irregular swellings, probably enlarged lymphatic glands.

**Urine:** Dark yellow, with pronounced urobilinuria, but with no protein and no sugar.

Wassermann reaction: Negative.

**Examination of blood:** Red cells per cmm: 1.17 mill. Haemoglobin (Haldane) 30 %. White cells 59,900. Platelets: 100,000. Icterus index (Meulengracht) 13. White cell differential count:

Lymphocytes: 95 %, Polymorph. nucl. neutroph. 3 %, Myelocytes  $\frac{1}{2}$  %, Metamyelocytes  $\frac{1}{2}$  %. Eosinophiles 1 %. Numerous giant neutrophil and multilobed neutrophil cells. The red corpuscles showed pronounced macro-mikro-aniso-poikilo-cytosis.

Basal metabolic rate: 156 %

Biopsy of a lymphatic node revealed lymph tissue with degenerated structure, where the usual tissue was replaced by lymphocytes. No necrotic parts, and no giant cells of the Reed-Sternberg type was present.

*Decursus morbi*: (see diagram) The first time after admission the patient was seriously ill: He felt tired, coughed and vomited. In this period he was treated with iron and arsenic, and was also given three transfusions of defibrinated blood, 2050 ccm. in all. This treatment did not have any lasting effect on his anaemia. General X-ray irradiation was then given. The swellings of the glands diminished, and the white cell count decreased towards normal values, but his condition remained serious, and he did not gain in weight.

It was now noticed that his anaemia was of a hyperchromic type with increased colour index, and the test-meal showed achlorhydria. One therefore decided to make a test with liver treatment and from Jan. 25. to Jan. 29. the patient received 100 ccm. liver-extract i. m. (Pernami). This resulted in a rapid increase in the number of reticulocytes, from 5 ‰ to 95 ‰. At the same time his anaemia gradually disappeared. He gained in weight and felt better.

By a regrettable omission sternal puncture was not performed till Febr. 2., 8 days after the treatment was started.

The examination of the sternal marrow revealed red corpuscles of greatly varying size, with numerous large, oval cells rich in haemoglobin, typical megalocytes. Further numerous microcytes and poikilocytes. The erythropoiesis was normo-macro-blastic with normal nuclear development, and without any increase in the number of proerythroblasts. No megaloblasts.

Normal morphology of the leucopoiesis, apart from an increase in multilobed neutrophil leucocytes with up to 7-8 lobes per cell. The number of lymphocytes was greatly increased and there was many Gumprechts shadows.

Sternal puncture was again performed on March 3. 1936:

There was a considerable change since Febr. 2.: The red blood cells had now normal appearance. No microcytes and only macrocytes were seen. The multilobed neutrophils were no longer demonstrable and both the erythropoiesis and the leucopoiesis appeared normal. The number of lymphocytes was greatly increased, as in the former examination.

A new puncture, on May 31. -1936 gave the same result as the puncture performed on March 5.

Later on the patient was again given injections of liverextract (Pernami) 100 ccm. He was further treated with daily doses of Ventriculin and received liver per os during his stay in the hospital. As the abdominal swelling remained unaltered, he was again given X-ray irradiation from March 3. to March 31.

At the time of discharge from the hospital the lymphatic glands were greatly reduced in size, only a few the size of hazelnuts were still palpable on the left side of the neck, in the right axillae, and the groins.

The liver remained enlarged. The edge was felt about 5 cm. below the costal margin. The spleen was not palpable. The red cells were 4.200.000, the haemoglobin was 88 %, the leucocytes 5.100 and the icterus index 3.

When leaving hospital he was advised to continue the treatment by eating liver. At the follow-up examination 2 months later the patient declared that he had been eating liver daily. He felt well and had been able to do light work on the farm. He was in good condition and weighed 72 kilos. The lymphatic glands were unaltered and there was no anaemia (haemoglobin 96 %, r. b. c. 5.000.000 w. b. c. 10.300).

The following months he was able to perform lighter work, but on Febr. 12. 1937 he felt ill and again called in his doctor. The doctor discovered a pleural effusion, and intended to perform a puncture on the following day. The patient's condition, however, grew rapidly worse, and he died the next day without further examination having been carried out.

#### *Comment.*

There is little doubt that the reported case is one of chronic lymphatic leukaemia, associated with pernicious anaemia. The

symptoms of *leukaemia* dates back to 1927—28, and the repeated successful treatments with arsenic and X-ray confirm the diagnosis. The diagnosis of *pernicious anaemia* is based on the following points: 1.) Marked hyperchromic anaemia, with high colour-index, megalomicro-poikilocytosis, and increase in the multilobed neutrophile leucocytes. 2.) Increased icterus index and urobilinuria. 3.) Glossy tongue. 4.) Achlorhydria. 5.) Optimal increase of reticulocytes after liver treatment.

During the meeting in Kiel I had the opportunity to show the blood-and sternal-marrow smears to Hans Schulten. In a letter dated July 16. th. 1936, he writes to me: "Die Diagnose der perniziösen Anämie, an der nach Ihrer Schilderung gar kein Zweifel sein kann, konnte ich allerdings nach der Knochenmarkausstrichen kaum mehr stellen. Da die Punktion aber erst einige Zeit nach Beginn der Lebertherapie gemacht worden ist, nimmt da nicht Wunder. Das einzige, was mir als perniziosaverdächtig auffiel war die ungewöhnliche Grösse einiger myeloischer Zellen. In den Blutbildern fand ich neben der Grösse der roten Zellen eine Reihe auffallend stark segmentierter Neutrophiler, wie ich das in dieser Art bei lymphatischer Leukämie nicht erinnere gesehen zu haben und wie es ja bei Perniziosa fast stets der Fall ist".

It is difficult to believe that the occurrence of the two diseases in the same person is a pure coincidence. Neither can one accept the view that the anaemia is caused by crowding out of the erythropoietic tissue by the leukaemia cells. To discuss the cause further is useless — as the cause of either of the two diseases are unknown.

More important is it to draw attention to the changes in the stomach. While achlorhydria is almost always present in pernicious anaemia, this is not the case in leukaemia. The author and B. Strandell have both previously stressed this point. Among 45 cases of myeloid and lymphatic leukaemia, 24 cases had free hydrochloric acid in the gastric juice. In our case we have achlorhydria. In old age achlorhydria is so common, however, that this sign cannot alone be responsible for pernicious anaemia. There must be other causes which are unknown. For the time being one has to be satisfied to remain on "die niedrige Stufe der Casuistik (Billroth)".

*Summary.*

A man 57 years old had from 1927-28 noticed enlargement of the lymphatic glands which decreased after repeated administration of arsenic. At the admission to the University Clinic A  $\frac{5}{12}$  -35 there was found enlargement of the lymphatic glands, enlargement of the spleen and liver, red corpuscles per cmm. 1.170.000, haemoglobin 30 %, white corpuscles 59.500 with 95 % lymphocytes and marked neutrophil hyper segmentation. Icterus index 13. The red corpuscles showed marked macro-micro-poikilocytosis. Ewald's test-meal: achlorhydria. The leukaemic symptoms reacted well to X-Ray treatment; but the anaemia persisted until liver treatment was started. This was followed by a optimal increase in reticulocytes and a gradual increase in haemoglobin and red corpuscles. On discharge the patient was feeling well — able to do lighter work. The author emphasizes the facts that indicate the presence of chronic lymphatic leukaemia and pernicious anaemia in the same patient and points out that only certain cases of leukaemia are accompanied by achylia, contrary to pernicious anaemia.

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## SLOUGHS FROM GASTRIC EROSIONS

By  
*J. C. Hawksley.*

### *Introduction.*

There are few conceptions of disease that vary so much in meaning amongst investigators in various branches of medicine as that of gastritis. Approach to a standard interpretation of the condition and its varieties must depend upon the histology of the gastric mucous membrane and it behoves clinicians, radiologists and users of the gastroscope to endeavour to bring their interpretations of phenomena into agreement with a set of standards based on pathology. The study of the gastric mucous membrane has led to descriptions of various types of lesion, amongst them the acute gastric erosion; this lesion is represented as a shallow breach in continuity of the surface epithelium, usually multiple, and extending into, but not through the glandular tissue. Such lesions heal by repair of the lost epithelium and are not associated with any special symptom unless it be haematemesis or melaena. By some the condition is held synonymous with acute ulcer and with erosive gastritis. Owing to its usually symptomless nature, the frequency of acute gastric erosion cannot be assessed by the clinician though its occurrence in post-mortem material and in stomachs resected by operation has been described by many. The experimental production of erosions of an analogous nature in animals was achieved by Bolton (1913). The production of an erosion is assumed to arise from superficial injury to or infection of, or from haemorrhage into the mucous membrane, with resultant separation of the devitalised piece, perhaps aided by peptic digestion. Unseparated sloughs were observed in the early stage of acute ulcers by Bolton (1913). Small areas of haemorrhage into the mucous membrane are not infrequently observed by

gastroscopists and these may represent places where an erosive process of this type is taking place.

The histological study of the small sloughs, which, unless completely digested before final separation has time to occur, must come away if erosions are to be formed, has been very incompletely carried out. Such pieces of separated mucous membrane were described by Einhorn (1894) from several cases of what he called "erosion of the stomach". These were obtained by gentle gastric lavage and Einhorn was satisfied that this process of lavage had not itself caused the lesion for he writes, "We have not to deal here with an incidental lesion caused by the tube, for, on the one hand, the lavage has been performed without any aspiration and by means of a soft tube; on the other hand, one could not observe in a casual lesion the constancy which is found here." Einhorn restricted his histological examination to identifying the glandular elements after mounting in glycerine. He described a further series of cases in 1899. His observations do not seem to have aroused the interest that their importance merited. In the first volume of his text book, *Gastro-Enterology*, Bockus (1946) has published microphotographs of a piece of aspirated mucous membrane. He describes the technique of morning aspiration and says that satisfactory pieces for microscopic study were only obtained from three out of eighteen patients suspected of gastritis. He does not point out, in contradistinction to Einhorn, that unless the trauma of tube or aspiration pulled off the pieces by force — an unlikely event as will be explained shortly — the bits of mucous membrane have represented sloughs that have separated into the resting juice and that they could not have done this without leaving a small raw area or erosion behind them.

#### *Procedure.*

When a patient is prepared for gastroscopy, it is sometimes the custom to aspirate the resting juice from the stomach with a soft rubber catheter before the gastroscope is passed. In two hundred consecutive gastroscopic cases so treated before the war of 1939—45, one or more pieces of mucous membrane were recovered from the resting juice in 21 cases. These pieces varied in size from that of a pin's head to about one centimeter in



Fig. 1.

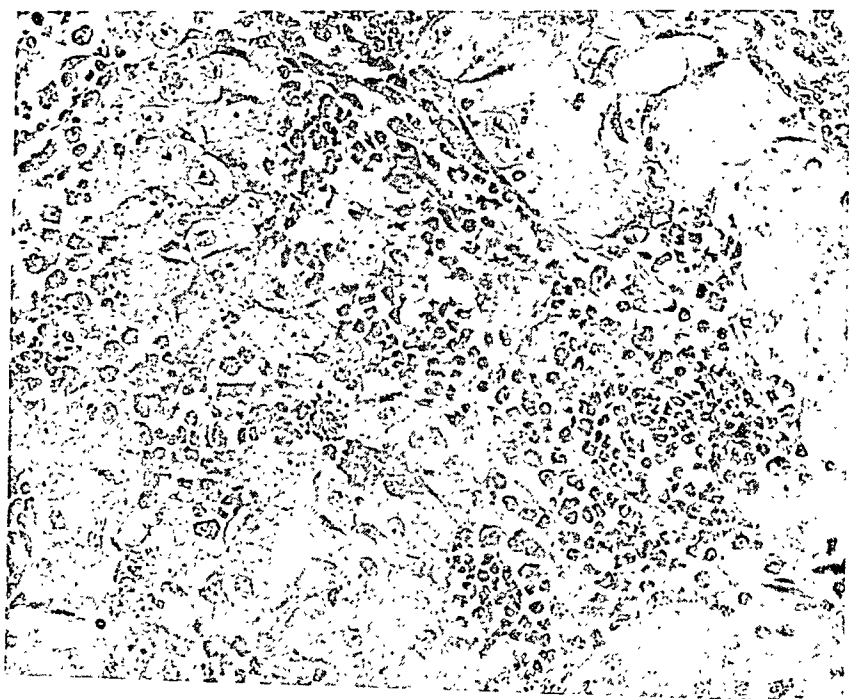


Fig. 2.



Fig. 3.

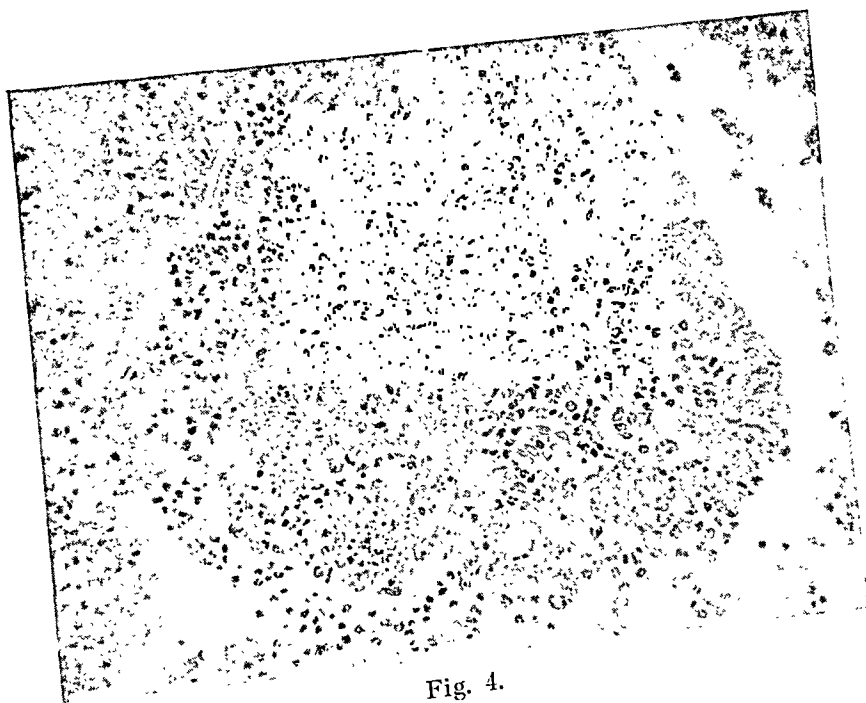


Fig. 4.

length. They came from cases that were being gastroscoped on account of symptoms of dyspepsia, and included cases of gastritis, ulcer, carcinoma and nervous dyspepsia; as there was no correlation apparent between the ultimate diagnosis and the recovery of pieces of mucous membrane, this aspect will not be further discussed. Since the war, the rate of recovery of these specimens has continued to be about 10 % of cases whose resting juice is aspirated.

The possibility that trauma by the aspirating tube or suction played a part in the separation of these pieces seems to be discounted by the following facts.

a. The process was carried out very gently.

b. No evidence of bleeding at all was seen either in the aspirated juice or on gastroscopy immediately afterwards except for a tiny trickle in one case. Removal of even a small piece should cause bleeding from so vascular a mucous membrane and has been shown to do so (though to no great degree) by the recently described technique of biopsy guided by gastroscopic observation (Kenamore, Scheff and Womack, 1946).

c. Attempts to remove pieces with the same rubber catheter from stomachs immediately after resection have failed. Even moderate trauma such as a scrape with the finger-nails is unsuccessful, so smooth and slippery is the surface.

### *Material.*

A brief description of these sloughs was given before the war (Hawksley, 1939) further and more detailed histological examination is now in process; it must suffice here to describe general appearances and the relation of the sloughs to erosive gastritis. As stated, pieces vary in size from a pin head to a centimeter in length. In all but a few, which were small and perhaps not representative of the complete initial slough, the interstitial changes produced by infiltration with lymphocytes and plasma cells indicated that the slough was from a mucous membrane which was the site of chronic gastritis. Figure 1 shows a photograph at seventy magnifications of a very small piece, and figure 2 an interstitial area of infiltration of round cells into a larger piece that has been magnified three hundred and forty times. A number, specially of the larger sloughs, showed that haemorrhage

hage had taken place into the superficial layers of the mucous membrane before separation. This is shown in figure 3 (25 magnifications) where an extensive superficial haemorrhage has occurred in a large slough which under higher magnification also shows considerable infiltration with inflammatory cells. In a number of sloughs, polymorphonuclear cells can also be seen interstitially and sometimes between the epithelial cells. Atrophic gastritis is apparent in several sloughs. In only one specimen so far has carcinomatous change been found (figure 4, 210 magnifications). In this, considerable polymorphonuclear infiltration can be noted in response to the spread of the neoplasm. It is of interest that Bolton (1913) described erosions occurring in the mucous membrane over areas where carcinomatous infiltration was taking place.

In a minority of specimens, goblet cells have been observed in the epithelium indicative of intestinal heterotopia, but neither Paneth nor argentaffine cells have so far been identified by appropriate staining in the few attempts so far made.

### *Discussion.*

The first point of interest has been to decide whether or not these pieces of mucous membrane are indicative of independent sloughing, or whether they are in part at least the result of trauma from gastric intubation. For reasons already given it is believed that they represent sloughed pieces of mucous membrane that have separated, and that in so doing they must have left erosions in their places. This was also Einhorn's opinion of the origin of his specimens. The fact that they are to be found (provided they are properly looked for) in about ten per cent of cases representing a mixed population of sufferers from gastric symptoms and that they are not apparently found with greater frequency in one gastric disorder than another suggests that erosive gastritis is a common event in such people, and also raises the possibility that it may be of more frequent occurrence than we believe in people who are not complaining of any gastric symptoms at all.

The second point of interest is that this series of sloughs is enabling us to study the gastric mucous membrane in ten per cent of our gastroscopy cases with almost the same intent as if

a deliberate biopsy had been performed. The differences between a slough and a biopsy in these cases are that the former may have come from any part of the stomach and possibly from a patch of particularly diseased mucous membrane, whereas a biopsy would be taken from some special region such as the neighbourhood of an ulcer or a carcinoma.

The two important points demonstrated by the histology of these specimens are that nearly all of them show a marked degree of chronic gastritis to have been present in the mucous membrane from which the slough came, and a small number show that haemorrhage had occurred locally into the mucous quences, by Professor Knud Faber.

For purposes of comparison and classification of gastritis, I have referred frequently to the book, *Gastritis and its consequences*, by Professor Knud Faber.

These notes represent a preliminary survey of material that is being more fully investigated at University College Hospital Medical School. I am much indebted to Mr. J. H. Bayley for the care he has given to preparation of the histological material.

### *Summary.*

The study of sloughed pieces of gastric mucous membrane is described and their significance in relation to gastric erosion is discussed.

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# POSSIBILITIES OF PREDICTING THE COURSE OF EPIDEMICS

By

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During autumn 1946 an epidemic of *parotitis epidemica* broke out in Copenhagen and rapidly manifested itself to become the second largest epidemic of this disease hitherto on record in Copenhagen. An estimation of the probable course of the epidemic was made according to the epidemic laws established by *Helge Petersen*. However, the relative epidemic constant could only be approximately established as being between  $4 \times 10^{-5}$  and  $2.5 \times 10^{-5}$ , due to the fact that only few epidemics of this disease had previously been registered in Copenhagen. Using the first figure, the estimated total number of cases would amount to between 7000 and 8000, while the constant  $2.5 \times 10^{-5}$  gave the result, that the expected number of cases would be between 9000 and 10000. Culmination was estimated to occur during the 48th week of the year and the maximum number per week at 564 — using 7500 as well as 9500 with their respective epidemic constants.

The culmination of the epidemic proved to occur during the 49th and 50th week with weekly figures of 595 and 591 (evened figures). Thus — for practical purpose — good agreement exists between the estimated and actual figures.

The difficulty in establishing the epidemic constant, however, raises the question of finding another method of estimating at a given time the number of individuals susceptible to an epidemic disease — in this case *parotitis*.

One of the equations set up by *Helge Petersen* is the following:

$$\gamma = \frac{n}{N} \times S$$

$\gamma$  denotes a factor determining the epidemic curve,  $n$  the number of cases included in the epidemic, and  $N$  the total number of inhabitants of the district in question.  $S$  denotes a constant for each particular disease. From this is derived the very important fact, that the epidemic curve can be defined, when the number of cases of the epidemic is known, i.e. the number of individuals susceptible to the disease at the outbreak of the epidemic. It would therefore be of interest to be able to know beforehand, or at least to estimate, the number of individuals susceptible to the disease at any given time out of a given population.

Undoubtedly, a certain amount of regularity exists as to the occurrence of epidemics. It is well known that two large epidemics hardly ever follow immediately one after the other. On the contrary, an epidemic generally becomes larger, the longer the lapse of time since the preceding epidemic.

Most pronounced this will be noted when an epidemic breaks out on virgin soil, i.e. in a district, where the disease in question has not appeared within living memory.

Considering conditions for *parotitis* these are rather easily perceived. *Parotitis epidemica* is a disease generally contracted in early years of life, and as a rule leaving immunity for life. The number of cases appearing during a series of years must therefore be proportional to the birth-rate. The number of cases during the first year of life being very small, partly due to inborn immunity, partly to less exposition, it is more correct to assume the annual addition of individuals susceptible to *parotitis* to be proportional to the number of children surviving the first year. In the following this is denominated the birth addition.

It is obvious that the number of susceptible individuals is lowest immediately following large epidemics. In order to get an impression of the total morbidity of a population concerning a definite, epidemic disease, it will therefore be most correct to compare the total number of cases having appeared during the time between the close of two large epidemics — separated by a considerable number of years — to the birth addition for the same period.

*Parotitis* hitherto having always proved to show a minimum

during the summer months and maximum during winter time, it is convenient to use the annual periods running from July to July. In July 1920 a comparatively large epidemic had just come to an end, and in July 1942 the hitherto largest *parotitis* epidemic had just terminated. During this interval of 22 years a total of 36,978 cases of *parotitis* were recorded. The birth addition during the same period was 228,000, which means that 16.2 %, or very near one sixth of the birth addition was reported as having had *parotitis*. Smaller epidemics terminated in July 1929 and in the summer of 1937. For these sub-periods can be mentioned, that from July 1929 13.6 % of the birth addition, from July 1929 to July 1937 13.3 % of the birth addition, and from July 1937 to July 1942 24.2 % of the birth addition was reported with *parotitis*. When the percentage for the two first periods is lower than for the last one, this can be explained by the fact that the latter was terminated with the large epidemic, which must be assumed to have included a larger part of susceptibles, while the chance of a susceptible avoiding the disease has probably been greater during the small epidemics.

Based on the above mentioned result, that a number equal to approximately one sixth of the birth addition will be reported annually as *parotitis*, the statistical information can be used to carry detailed account with the number of individuals susceptible to *parotitis* at any time existing in the population of Copenhagen. Such an account is shown on the following table. This table also shows the size of the part the susceptible individuals form of the entire population as per 1st July of each year. It will be noted that an epidemic has never broken out, when the proportion between the number of susceptible persons and the total number of the population is less than 0.84 %, and on the other hand this proportion has never exceeded 1.72 % without being followed by an epidemic. Between these figures we find that interval within which exists such concentration of susceptibles necessary to bring about conditions for the development of an epidemic of *parotitis*, according to our experiences during the past 22 years.

In the following it will be explained how this result can be used in forecasting the size of an epidemic. Supposing that no susceptible individuals were left after the large epidemic of 1942,

the number of susceptibles the following years can be seen in the table. Per July 1st, 1946, 8,100 susceptibles were found or 1.11 % of the population, i.e. within the interval, where an epidemic is likely to break out. Should an epidemic break out during the following year, one sixth of the birth addition of this year will have to be included, and the amount being 2300, the total number of susceptible individuals will be 10,400 as per 1st July, 1947. A possible epidemic is therefore not likely to exceed this number. In reality a *parotitis* epidemic broke out in the autumn of 1946, and has up to its end (July 1947) reached a total of 10,104 cases — in good accordance with the forecast.

Turning to *morbilli* we find that conditions show still more regularity. *Morbilli* epidemics have as a rule appeared every two or three years. They too culminate during the winter months, wherefore it will also be best for this disease to use the annual period from July to July. In July 1920 a considerable *morbilli* epidemic had just finished, and a very large epidemic came to an end just before July 1938. During the time from July 1920 to July 1938 82,183 cases of *morbilli* were reported. The birth addition during the same period amounted to 179,000, i.e. 45.9 % of the birth addition was reported with *morbilli*. Dividing the period in smaller intervals after the close of other *morbilli* epidemics it was found, that from July 1920 till July 1928 a number equal to 43.7 % of the birth addition was reported as

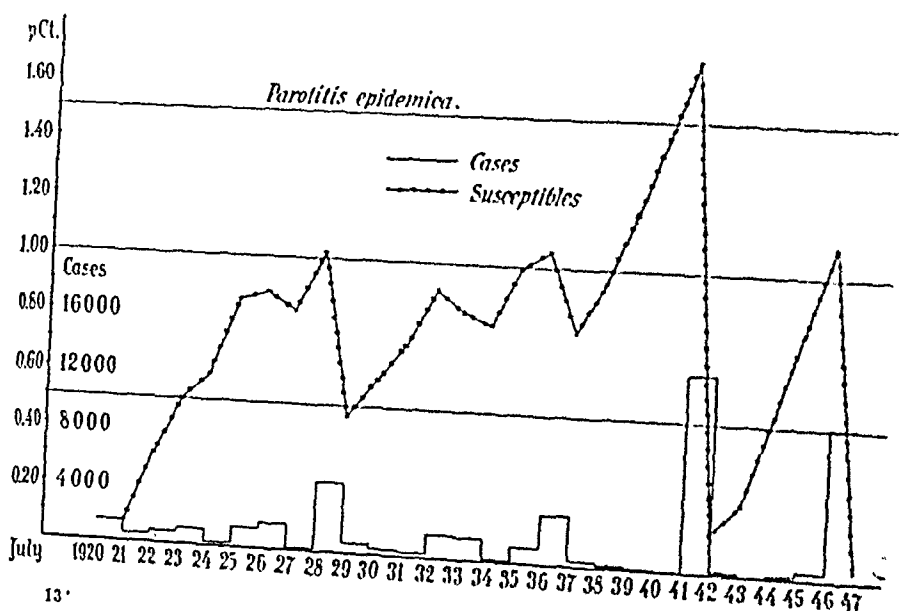


Table 1.  
*Parotitis epidemica.*

Interval from July 1920 to:			Birth addition Total 16,7% (= 1/6)	Cases of parotitis	Susceptibles Number in % of popula- tion	Size of epi- demic the following year
July 1921	....	11000	1833	1369	464	0.07
— 1922	....	23000	3833	2052	1781	0.31
— 1923	....	35000	5833	2943	2890	0.50
— 1924	....	45000	7500	4036	3464	0.59
— 1925	....	56000	9333	4324	5009	0.85
— 1926	....	66000	11000	5756	5244	0.88
— 1927	....	75000	12500	7588	4912	0.82
— 1928	....	84000	14000	7828	6172	1.02
— 1929	....	93000	15500	12622	2878	0.47
— 1930	....	103000	17167	13465	3702	0.60
— 1931	....	111000	18500	13997	4503	0.72
— 1932	....	121000	20167	14422	5745	0.91
— 1933	....	129000	21500	16119	5381	0.84
— 1934	....	138000	23000	17762	5238	0.80
— 1935	....	148000	24667	18013	6654	1.00
— 1936	....	158000	26333	19198	7135	1.06
— 1937	....	169000	28167	22750	5417	0.79
— 1938	....	179000	29833	23188	6645	0.96
— 1939	....	191000	31833	23455	8378	1.20
— 1940	....	203000	33833	23616	10217	1.46
— 1941	....	215000	35833	23725	12108	1.72
— 1942	....	228000	38000	36978	1022	0.14
from						
July 1942 to:						
July 1943	....	12000	2000	275	1725	0.24
— 1944	....	26000	4333	458	3875	0.54
— 1945	....	40000	6667	665	6002	0.82
— 1946	....	55000	9167	1070	8097	1.11

*morbilli*, from July 1928 till July 1935 48,9 % and from July 1935 till July 1938 45.8 % — in other words practically the same percentage. This proves the statistics on *morbilli* to be of great accuracy, and the percentage of cases reported to have been very even during the period under observation.

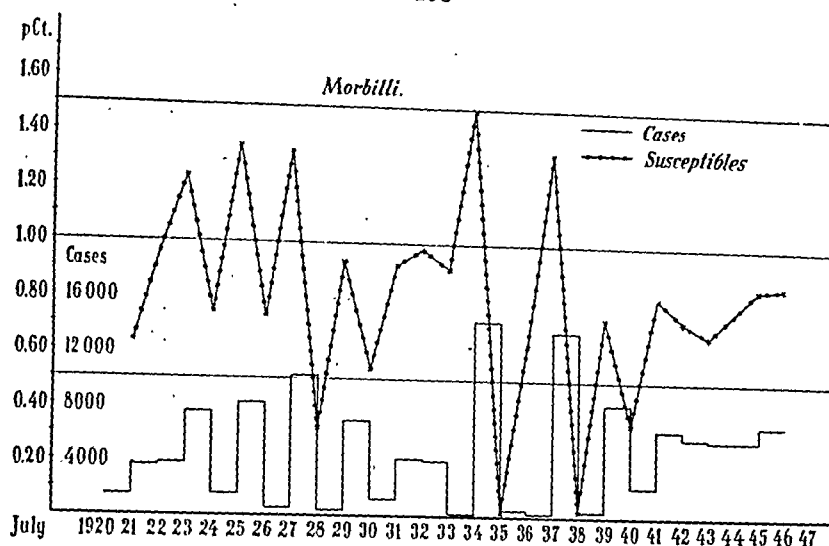
Comparing the number of *morbilli* susceptibles to the entire population the percentage has been 1.50, at the highest, and no epidemic has broken out, without this percentage having been above 0.92. Calculations for the following years have shown, that some minor epidemics have broken out, when the

Table 2.  
*Morbilli.*

Interval from July 1920 to:	Birth Total	addition 46 %	Cases of morbilli	Susceptibles Number	in % of popula- tion	Size of epi- demic the following year
July 1921 ....	11000	5060	1532	3528	0.63	
— 1922 ....	23000	10680	5156	5524	0.96	
— 1923 ....	35000	16100	8894	7206	1.24	7481
— 1924 ....	45000	20700	16375	4325	0.74	
— 1925 ....	56000	25760	17861	7899	1.35	8177
— 1926 ....	66000	30360	26038	4322	0.73	
— 1927 ....	75000	34500	26508	7992	1.34	10195
— 1928 ....	84000	38640	36703	1937	0.32	
— 1929 ....	93000	42780	37112	5668	0.93	6995
— 1930 ....	103000	47380	44067	3313	0.54	
— 1931 ....	111000	51060	45288	5772	0.92	4155
— 1932 ....	121000	55660	49443	6217	0.98	4068
— 1933 ....	129000	59340	53511	5829	0.91	
— 1934 ....	138000	63480	53698	9782	1.50	14285
— 1935 ....	148000	68080	67983	97	0.01	
— 1936 ....	158000	72680	68442	4238	0.63	
— 1937 ....	169000	77740	68535	9205	1.34	13648
— 1938 ....	179000	82340	82183	157	0.02	
from						
July 1938 to:						
July 1939 ....	12000	5520	397	5123	0.73	8287
— 1940 ....	24000	11040	8684	2356	0.34	
— 1941 ....	36000	16560	10895	5665	0.81	6460
— 1942 ....	49000	22540	17355	5185	0.73	5907
— 1943 ....	61000	28060	23262	4798	0.67	5768
— 1944 ....	75000	34500	29030	5470	0.76	5688
— 1945 ....	89000	40940	34718	6222	0.85	6841
— 1946 ....	104000	47840	41559	6281	0.86	

percentage has been slightly lower, down to 0.67. The zone — in which an outbreak of *morbilli* may be expected — is therefore between 0.67 % and 1.50 % of susceptibles in the population, but only when the percentage has been 1.34 or more, have nearly 100 % of the susceptibles been attacked during the epidemic.

On the diagrams are shown the number of susceptibles in percentage of the population (the concentration) and the size of the actual epidemics. The relation between the two is clearly seen. If the concentration is high, large epidemics will break



out, if it is low, there will be small epidemics or none. It will be seen that it is rational to characterize as an epidemic such number of cases that will be able to reduce the number of susceptibles or to keep it constant. (Tables and Fig. 1 and 2.)

In regard to *influenza* conditions are different, as this disease does not leave immunity for life and does not have the character of a children's disease. The addition to the susceptibles is therefore not proportional to the birth addition, but to the size of the entire population. As to longer periods the number of individuals attacked by *influenza* is quite constant in relation to the population, as the following figures will show:

From July 1920—July 1929: 200,500 cases = 3.77 % yearly of popul.

From July 1929—July 1933: 128,300 cases = 5.03 % yearly of popul.

From July 1933—July 1946: 325,240 cases = 3.92 % yearly of popul.

Taking these periods under one it means an average percentage of 4.2 of Copenhagen's population yearly gets *influenza*. A detailed account from year to year does not, however, show such good agreement between the estimated number of susceptibles and the actual number of patients as is the case with *morbilli* and *parotitis*. The reason for this may quite naturally be due to the fact that the diagnosis of *influenza* is not quite as sure as that of the two children's diseases. Undoubtedly, a number of cases of other diseases has been included in the

statistics of influenza, f. inst. tracheobronchitis, viruspneumoniae, febrilia due to other causes, and possibly gastro-intestinal cases. More detailed *influenza* statistics will probably yield valuable help in this respect. The social importance of the *influenza* might justify a more extended cooperation on this point between statistics and clinic.

The scope of this work is to show that — though apparently capricious in their occurrence — the epidemics, viewed over a long period, are subject to a considerable degree of regularity, which fact quite naturally is most pronounced in case of diseases easily diagnosed, such as *morbilli* and *parotitis* for which immunity conditions are so clearly defined. The population of a town is steadily receiving a certain birth addition, and these new individuals must be immunized like the rest of the population. This is effected in the manner, that when the concentration of susceptible individuals has reached a certain point, there is a chance of an epidemic, and the greater the concentration the greater the chance. Also other things influence an outbreak of an epidemic, e. g. the season of the year. If an epidemic has started, its course will be according to the laws stated by *Helge Petersen*.

According to the above it seems to be within the possibility of the medical statistics 1) in regard to certain diseases to keep account of the number of susceptibles to be found at any time in a population, and as a consequence thereof to know beforehand the maximum size of a possible epidemic, 2) to a certain degree to be able to judge the chance of the outbreak of an epidemic, and 3) — when the epidemic has broken out — to predict approximately its course and time of culmination.

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## STREPTOCOCCAL PNEUMONIA

By

*Kurt Iversen, M.D.*

Previously, as a rule, the pneumonias were classified after the pathologic-anatomical processes and their extension as indicated by the findings on clinical examination, whereas in more recent years these diseases are being grouped to a large extent after their bacteriological aspects. Several clinicians employ a combination of these two ways of classification — which may be said to offer certain advantages.

In the pathologic-anatomical classification distinction is made between lobar and lobular pneumonia (or croupous pneumonia and bronchopneumonia). The clinical picture of typical lobar pneumonia is extraordinarily characteristic. Here in Denmark it is produced most often by pneumococci of types 1,2 and 7 (*Nissen* (8)) but, as a matter of fact also any of the other types may give rise to lobar pneumonia. As to the occurrence of the pneumococcus types in Denmark, the reader is referred to the monograph of *Vammen* (10).

Lobular pneumonia (bronchopneumonia) is far less characteristic in its clinical features. Often its onset is more insidious, sometimes as a complication of another lesion. Also this form of pneumonia is produced most often by pneumococci, not infrequently through autoinfection, as the bacteria from the throat — where they are present in about one half of all persons — invade the air passages, giving rise to inflammatory processes here. As is well-known, secondary pneumococcal pneumonia is a common complication in measles and whooping cough.

After serotherapy in pneumonia with type-specific immune serum had been rendered practicable through *Cooper's* (2) demonstration and isolation of serologically well-defined pneumococcus types, in the middle thirties it was adopted in many

clinics to classify the pneumonias according to whether or not they were produced by pneumococci — a classification which primarily served a therapeutic purpose.

A greater majority of all cases of pneumonia (about 80 %) are produced by pneumococci. Lately, however, an increasing interest has been taken in pneumonias produced by other microbes or viruses. So, now it may be said to be most expedient to characterize a given case of pneumonia by recording its etiology at the same time — *e. g.*, lobar pneumonia (or bronchopneumonia), pneumococcal, type 7; in another case: streptococcal bronchopneumonia. In this way, information is given about the character of the pneumonia and its etiology.

In the following a description will be given of streptococcal pneumonia, which appears to present a rather characteristic clinical picture with certain particular features, which entitle this morbid condition to be looked upon as a specific nosographic unity *per se*.

In 1891 *Finkler* (5) was the first to describe the streptococcal pneumonia as a clinical entity. The disease may appear partly as a primary lesion, partly as a secondary affection following measles or influenza. Most often it is sporadic, but sometimes it may appear epidemically in epidemics of measles or influenza. Indeed, the most important observations on streptococcal pneumonia have been made during such epidemics — *e. g.*, by *Finkler* (5) during the influenza pandemic in 1889, and by *MacCallum* (7) in 1919 during a large epidemic of measles among recruits.

*Etiology.* — The disease is produced by hemolytic streptococci belonging to *Lancefield's* group A, occurring in the nasopharynx of normal persons (*Ernst* (4)). It does not look as if any particular type of the hemolytic streptococci would be particularly inclined to produce pneumonia.

*Occurrence.* — In comparison to pneumococcal pneumonia, streptococcal pneumonia is not particularly common. *Keefer, Rantz & Rammelkamp* (6) think that 3–5 % of all pneumonias are due to hemolytic streptococci. Their calculation may hardly hold true, however, as we cannot reckon for sure that all the

cases which they designate as streptococcal pneumonia really had been due to streptococci. As in pneumococcal pneumonia, it can by no means be taken for granted that the bacterium isolated from the expectorate really is the etiological agent. In order to be quite sure that a given case really involves a streptococcal pneumonia, the presence of streptococci must have been demonstrated in the pleural exudate or on direct lung puncture. This demand has not been met consistently. Growth of hemolytic streptococci as the only form of bacteria in throat cultures tell us nothing about the etiology of the pneumonia, as hemolytic streptococci are found very frequently in the throat of persons in good health.

In the writer's material, comprising 582 pneumonic patients in all age-classes, streptococcal pneumonia was diagnosed with absolute certainty only in 3 cases (about  $\frac{1}{2}$  %). But it is to be emphasized that no consistent search for the etiological agent was made in all these cases.

*Pathologic Anatomy.* — Streptococcal pneumonia is characterized, above all, by being an interstitial bronchopneumonia with chiefly interstitial infiltration of the lungs (MacCallum (7)). The lungs are bluish red, with palpable nodes varying in size. On section these nodes are found to consist of masses of yellow material round terminal bronchioli from which pus can be pressed out. These groups are surrounded by a hemorrhagic zone. The rather abundant pleural exudate is most often motley, sometimes purulent. Microscopically the terminal bronchioli are found to be filled with polymorphonuclear leukocytes. The walls of the bronchioli and adjacent alveoli are markedly infiltrated with leukocytes and lymphocytes. A thorough description of the pathologic-anatomical features of streptococcal pneumonia has been given in a monograph of Reimann (9).

*Symptoms.* — For illustration of the symptomatology it will be appropriate in the following to give in abstract some case records of patients suffering from streptococcal pneumonia.

#### *Case 1.*

Male, aged 57 (Record No. 709/40).

17 years before the patient was operated on for a severe degree of frontal and maxillary sinusitis. Since then he has had chronic

frontal and maxillary sinusitis, which he has kept down by daily nasal irrigation.

Two weeks before admission he gradually became poorly with cold, cough, frontal headache, tiredness and elevation of the temperature to about 38° C.

On admission (on 6/2/40) the patient did not look very ill; no dyspnea or cyanosis. Physical examination revealed no acute changes in the throat, but auscultation of the lungs showed signs of pneumonia from the right side, which was confirmed on roentgenographi.

Numerous examinations of the sputum showed no pneumococci or tubercle bacilli, and blood cultures, made on the day of admission showed no growth; nor could any pneumococcus and antibody be demonstrated in the blood. The patient was treated with sulfapyridine, 2 + 1 g. every 4 hours. As the temperature curve kept taking a markedly septic course, on 28/2 *pleural puncture in the right infrascapular region* was performed, with evacuation of a scanty amount of thick yellowish pus, which on cultivation proved to contain *hemolytic streptococci of group A in pure culture*.

As the temperature remained as before, treatment was instituted with sulfanilamide, 1 g.  $\times$  3 daily for 11 days, with good effect on the temperature, which gradually subsided to a normal level. On discontinuance of the remedy the temperature rose again abruptly on which account the patient was given sulfanilamide again for 13 days, whereafter the temperature kept at a normal level, and no fluid was obtained on pleural puncture. The patient was poorly and dyspneic for a long time, and he could not be discharged until 2½ month after admission. Repeated ambulatory examinations showed pronounced roentgenological changes in the lung, chiefly in the form of fibrosis as long as one year after the discharge.

This patient thus had an attack of bacteriologically verified streptococcal pneumonia. Correspondingly, his blood gave a strong positive antistreptolysin reaction, with a titer of 640, 910, 1200, 1100, and 6 months later, 415.

### Case 2.

Male, aged 42 (Record No. 707/43).

Past history of good health. One week before admission, the patient caught a cold, with sore throat and general indisposition. Two days before admission, he suddenly had an attack of chills with fever and stitching in the chest, accompanied by dyspnea.

On admission (on 6/3/43) he was exhausted, pale-cyanotic and rather dyspneic. Temperature 39.2° C. Pulse 96. Respiration 48. There was intense redness of the fauces and lacunar patches of

exudate on the tonsils. Auscultations of the lungs revealed pneumonia at the base of the right lung.

The patient was at once given sulfathiazole, 1.5 g. every 4 hours. On the following day the patient was more exhausted, with considerable cough and mucopurulent expectorate. Pleural puncture yielded yellowish-green pus from the pleural cavity. *Microscopy of, and cultivation from, the pleural exudate showed hemolytic streptococci of group A, type 6, in pure culture.* No pneumococci were found in the sputum. Repeated pleural punctures on 7/3 and 12/3 showed the pleural exudate to have become motley, serous, still containing hemolytic streptococci of group A, type 6, on which account chemotherapy was continued alone (sulfamethylthiodiazole). The temperature kept at a high level, and the patient was intoxicated and exhausted. Pleural puncture on 16/3 in the right infrascapular space yielded pure pus. The patient therefore was transmitted to the Surgical Department, where pleurotomy and drainage ad modum Bülow was performed.

The postoperative course was uncomplicated, and the patient was discharged two months after admission.

### Case 3.

Female, aged 35 (Record No. 73/47).

Apart from relapsing sinusitis, the patient gave a past history of good health.

One week before admission she caught a cold, with marked purulent coryza, sore throat, debilitation, frontal headache and fever (about 38.5° C.). Gradually she was getting more and more poorly, with increasing cough and mucous expectorate; on the day before admission she had chills.

On admission (on 19/11/46) the patient was markedly febrile, slightly cyanotic and dyspneic, besides somewhat intoxicated. Temperature 39.5° C. Pulse 116. The tonsils were red and swollen. Otolgic examination showed evidence of acute maxillary sinusitis. Auscultation of the lungs showed signs of pneumonia on the right side; and roentgenography of the lungs showed small woolly densities, signifying small scattered infiltrations.

The patient was given sulfathiazole, 1 g. every 4 hours — without any particular effect. The temperature kept varying round 38—39°, and the patient still appeared intoxicated.

Examination of the sputum showed no pneumococci, but cultures showed growth of hemolytic streptococci of group A, type 1. No tubercle bacilli.

A sample of serum, taken on 27/11, gave a positive cold-agglutination reaction with a titer > 64. Thus the patient had a virus pneumonia; for the sake of completeness, however, pleural puncture, in the right infrascapular space, was performed on 28/11, but yielded

only a little blood-tinted serous fluid which on cultivation was found to contain also *hemolytic streptococci group A, type 1, in pure culture* — the same type as had been found in the sputum. In this case, then, there was also a simultaneous streptococcal pneumonia, on which account treatment was instituted with penicillin + adrenaline, 100,000 units  $\times$  3, in response to which the temperature subsided slowly during the following week, and, at the same time, the general condition of the patient improved.

Still, the patient kept being tired and exhausted for a long time, and she was not feeling well enough to be discharged until 13/1/47, i. e., 2 months after admission.

In the following two cases the diagnosis of streptococcal pneumonia was not verified bacteriologically, but the course of illness and the outcome of the antistreptolysin reaction were rather suggestive of streptococcal pneumonia.

#### Case 4.

Male, aged 50 (Record No. 943/40).

Through the later years the patient had been troubled with recurrent attacks of bronchitis.

One week before admission he caught a cold, with sore throat. Gradually he was getting worse, had cough and rise in temperature to 39 °.

On admission (on 4/5—40) the patient was not particularly exhausted, though somewhat cyanotic, coughing and producing a purulent expectorate. The tonsils were red and swollen and mucus was found in the rhinopharynx. Auscultation of the lungs revealed a bilateral pneumonia, for which the patient was given sulfapyridine, 1 g. every 4 hours, which resulted in a lytic fall in the temperature in the course of 8 days and a slow improvement of his general condition. On pleural puncture, on 6/5, only a few drops of serous fluid were obtained, and this yielded no bacterial growth on cultivation. On the other hand, examination of his sputum showed repeatedly the presence of pneumococci of type 18, but unfortunately no examination was made for hemolytic streptococci until a few days before the discharge, when no hemolytic streptococci could be demonstrated.

The case of this patient is not clear-cut. Pneumococci of type 18 were found in the sputum, it is true, but not in the pleural fluid. From experience this pneumococcus type is known to be

pathogenic but seldom. That the lung lesion possibly was due to a streptococcal infection is evident from the *antistreptolysin reaction*, the titer of which was increasing during the course of the pneumonia (on 18/5—20/5—13/6 respectively 150—360—555).

#### Case 5.

Male, aged 34 (Record No. 955/43).

At the age of 22 years, rheumatic fever, without cardiac complications.

Three weeks before admission, attack of angina with fever up to 40°. He was treated at home with sulfathiazole, after which the fever subsided. Since that illness, however, he kept feeling poorly, with sore throat. Two days before admission he had stitching in the chest together with fever and cough.

On admission (on 13/3—43) the patient was markedly febrile, somewhat dyspneic, but not particularly exhausted. Temperature 39.5°. Pulse 94. Considerable redness of the fauces, but no patches of the tonsils. Auscultation of the lungs revealed pneumonia on the right side, for which the patient was treated with sulfathiazole, 2 + 1 g. every 4 hours, with good effect of the temperature, which became normal within a couple of days.

Examination of the sputum showed no pneumococci or tubercle bacilli. No pleural or pulmonary puncture was performed.

Also in this case the diagnosis of streptococcal pneumonia was not verified bacteriologically, but the diagnosis is highly probable, as the *antistreptolysin reaction* was distinctly increased, with a tendency to rise in the course of the pneumonia (on 25/3—3/4 and 10/4 the values obtained for AST were respectively 455—575—720).

*Diagnosis.* — These case records present some characteristic features met with in most cases of streptococcal pneumonia. Generally these patients have had a cold, sinusitis or regular attack of tonsillar angina shortly before the onset of pneumonia. The pneumonia itself commences gradually, not suddenly — as does lobar pneumonia. The temperature begins to rise, and coughing commences, with pain in the chest, and increasing affection of the general condition. The fever rises to a high level, and it may persist as a continuous fever, or it may become remittent. Most often the tachycardia is rather pronounced. As

a rule, the patients are very exhausted, dyspneic and cyanotic. Examination of the blood usually shows leukocytosis, whereas bacteriemia is rare; the auscultatory findings are the same as usually found in pneumonia, although the processes in the lungs generally are more extensive and most often involve both lungs. The lung lesion is said strikingly often to be complicated by the presence of the pleural exudate, which rather frequently develops into regular empyema. As often seen in streptococcal infections, as stated by Eriksson (3), the lesion is sometimes associated with the appearance of arthralgia that may turn into typical rheumatic polyarthritis. Further there is an increase in the antistreptolysin reaction, which in some cases may attain a very high titer.

In favorable cases the temperature falls by lysis within from two to three weeks, and the symptoms subside at the same time.

*Differential Diagnosis.* — It is most difficult to differentiate this lesion from septic infarction in the lungs during a streptococcal bacteriemia. Here attention has to be paid especially to the initial symptoms, as pulmonary infarction sets in quite suddenly with stitching in the chest, cough and sanguinolent expectorate, whereas streptococcal pneumonia usually develops gradually, following a streptococcal infection in the upper air passages (angina or sinusitis).

*Treatment* with sulfonamides should be instituted at once, but in most cases this is not sufficient. Probably penicillin or streptomycin is more effective, but so far nothing definite has been reported on this point. It has been suggested to treat such patients with antistreptococcus serum (Amoss (1)) or with scarlatina convalescent serum, but it is rather doubtful whether that therapy is of any value. Considering that so far about 30 different types of hemolytic streptococci have been demonstrated, it seems reasonable to expect that serotherapy in these cases requires a type-specific immune serum — and this appears not to have been tried yet.

*Prognosis.* — In comparison to lobar pneumococcal pneumonia, the prognosis in cases of this kind appears to be serious. The lethality varies somewhat, depending on the age of the patient, the premorbid state of the patient, and the extent and complica-

tions of the process in the lungs. According to the literature, the case mortality appears to be between 35 % and 60 %. During epidemics it is claimed to be even higher. Owing to the interstitial character of the pneumonia, it often gives rise to later development of bronchiectasis, emphysema and pulmonary fibrosis.

### *Summary.*

A report is given of three cases of pneumonia produced by hemolytic streptococci (demonstrated in the pleural exudate or by lung puncture). On the basis of these cases and the recent literature, a brief description is given of the clinical picture of streptococcal pneumonia, which shows certain characteristic and special features that allow the disease to be looked upon as a clinical entity.

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## THE EFFECT OF GASTRECTOMY ON THE BLOOD PICTURE AND ON THE RIPENING INDEX OF RETICULOCYTES IN RATS

By

*Erik Jacobsen and C. M. Plum.*

A relation between gastric function and the formation of red blood cells is well known. Earlier clinicians suggested that the atrophy of the stomach was responsible for the pernicious anaemia, but *Castle* first showed that this disease is due to a nutritional deficiency conditioned by a defect in the gastric secretions. Shortly thereafter *Sturgis and Isaacs* introduced the use of desiccated hog stomach in the treatment of pernicious anaemia and showed that this treatment is able to abolish all symptoms of lack of erythrocyte formation. *Meulengracht* subsequently demonstrated that the specifically anti-pernicious anaemia activity of pig stomach is largely confined to the pyloric region. All these facts are described in every textbook of medicine.

In man total gastrectomy is often followed by a severe anaemia. In most cases this is microcytic in type, but a number of cases are described in the literature where a genuine pernicious anaemia has developed.

In experiments employing gastrectomy in dogs, swine, cats, monkeys and rats, all investigators agree that the operation is followed by a more or less pronounced anaemia, which is accentuated under conditions where the requirement for the formation of red blood cells is augmented as after repeated blood lettings, in pregnancy, or after liver damage. A blood picture corresponding to that of human pernicious anaemia is never seen.

Other symptoms of gastrectomy are also described, the most

significant of which are inhibition of growth, emaciation, changes in skin and hair, and more or less severe neurological abnormalities and morphological changes in the central nervous system; disturbances in bone calcification are sometimes found. *Petri* and his collaborators use the term *gastroprival pellagra* to describe this condition. The majority of papers dealing with experimental gastrectomy are surveyed by *Petri and Jensenius* (1941) to whom we refer for further details. Several authors have shown that extracts from the livers of gastrectomized animals have no therapeutic effect in human pernicious anaemia.

Siminarily symptoms, especially the anaemia in gastrectomized animals cannot be abolished by treatment with liver extract. High doses of iron salts have only an incomplete effect. Some authors find that the combination of iron and liver extract is of no more benefit than is found after iron alone.

In this laboratory *C. M. Plum* (1942) found a principle in plasma and liver extracts, which accelerates the ripening of reticulocytes in vitro. In a series of papers it was shown that increased erythropoietic activity is accompanied by increased amounts of the ripening principle in plasma (*C. M. Plum* 1943), and that patients with untreated pernicious anaemia have a diminished amount of ripening principle in their plasma (*Stefan Jorgensen and C. M. Plum* (1943), *Ruth Plum* (1943—1947)). A relationship between blood formation and the reticulocyte ripening principle is thus possible.

The reticulocyte ripening principle has been found to consist of at least two fractions, one thermostable and the other thermolabile. The former fraction is identical with tyrosine (*Erik Jacobsen and C. M. Plum* 1942) or some tyrosine derivative (*Inger Gad, Erik Jacobsen and C. M. Plum* 1944). It is probable that the tyrosine and the thermolabile fraction are linked together in the reticulo-endothelial system and thus form the reticulocyte ripening principle found in plasma (*Erik Jacobsen and C. M. Plum* 1943).

*C. M. Plum* (1944 I, II) showed that gastric tissue and gastric juice contain the thermolabile fraction in great amounts, since extracts from stomach tissue show a considerable ripening effect on reticulocytes when activated by tyrosine. *Erik Jacobsen*

(1944) has isolated a part of the thermolabile fraction from gastric tissue and found it akin to xanthine.

It was therefore of great interest to test the effect of gastrectomy on the ripening activity of the plasma and to compare this with the other symptoms of gastrectomy. These studies, employing rats as experimental animals, are described in the present report.

### *Technique.*

Gastrectomy in rats is referred to by *Maison* and his collaborators (1933) who found subsequent symptoms corresponding to those described above. Their paper, however, gives no description of this rather difficult operation.

The technique employed by us differs in principle from that described by *Maison* and by *Higgins* as we only excise the part of the stomach containing the gastric glands, leaving the oesophageal part *in situ*.

Rats weighing 200—240 gram are anaesthetized with ether and fixed on their backs to the operating table. An incision of 3—4 cm. is made in the mid line of the upper abdomen; the duodenum is separated from the stomach just caudal to the pyloric region between two clamps, and the duodenal end closed with a buried suture. The lesser omentum is then ligated and cut. Two artery clamps are next placed across the stomach from the greater curvature just to the right of the oesophagus, separating the two clearly distinct parts of the stomach: the pale left whitish part having no digestive glands, and the right reddish part containing all the peptic glands. The stomach is then cut between the two clamps and the excised part of the stomach is removed. The upper two thirds of the opening in the remaining part of the stomach are now closed with a thin suture and, by means of a suture, covered with the duodenal stump. A 2—4 mm. longitudinal incision is then made in duodenum and an end-to-side anastomosis is made between this incision and the part of the stomach incision not closed by the suture. After placing about 20 mg. sulfathiazol in the peritoneal cavity the abdominal wall is closed in two layers with sutures. After the operation, which with some practise can be done in 20—25 minutes, the animals received 10 ml. saline subcutaneously

and were placed at 32° for a few hours. The mortality after the operation was rather great. Some of the rats developed abscessae generally localized between the liver and the anastomosis. When such abscessae were observed in the autopsy the animal was discarded from the experimental protocol. Not a few of the operated animals died of pneumonia. In those rats surviving the operation 1—2 months, the remaining part of the stomach was found to be enlarged and formed a real "stomach" of approximately the same size as the normal stomach. Histological control showed that the mucosa contained only a few digestive glands covering less than 10 percent of the whole stomach area, while the mucosa of the normal stomach has more than 75 percent of its area covered with peptic glands.

The effects of the operation confirmed the descriptions given in the literature (*Maison et al. (1933) and Higgins (1947)*). The blood showed a lowered haemoglobin level, microcytosis, and a reticulocytosis. All these effects are seen from the subsequent tables. An interesting and hitherto unreported feature is the decline in iron reserves, manifesting itself in a depigmentation of the incisors and a decrease in liver iron. These observations are described separately in a paper by *J. J. Pindborg and C. M. Plum (1946)*.

The effects on the reticulocyte ripening factor in plasma are shown in table 1. It is seen that the ripening index is decreased markedly after gastrectomy, but returns to normal after the addition of tyrosine to the plasma. Since the stomach glands are known to produce the thermolabile factor in the ripening complex, was to be expected that a decrease in ripening activity in plasma after gastrectomy due to a decrease in the thermolabile component might occur, and that the addition of tyrosine should be without further effect. Nevertheless this decrease in ripening index after gastrectomy which is abolished by the addition of tyrosine or tyrosine derivatives does not differ from what is seen in patients with untreated pernicious anemia and with certain gastric diseases where the ripening index in the plasma is found to be low, but becomes normal after addition of tyrosine. Consequently it must be supposed that the gastric mucosa is not the only source of the thermolabile fraction of the ripening principle. As a matter of fact *Bohn, Landboe-Chri-*

*stensen and Plum* (1945) found the mucosa of the duodenum and of the proximal part of jejunum to be very rich in the thermolabile fraction. The gastrectomy, therefore, removes only a portion of the tissues producing the thermolabile factor, not enough to give a marked decrease in ripening activity on addition of tyrosine. The decrease found may be caused by a deficiency in either tyrosine metabolism or in the mechanism of linkage between the thermolabile and thermostable fractions of the ripening principle in plasma.

The findings following gastrectomy in our experiments and in those of earlier investigators can be summarized thus: (I) a microcytic anaemia, (II) an iron deficiency, (III) a deficiency in the "tyrosine" fraction of the reticulocyte ripening factors in the blood and (IV) a reticulocytosis.

Two series of experiments with gastrectomized rats were next done to determine whether or not any of the above findings were mutually independent. *A priori* it is possible that the anaemia is due partially at least to the iron deficiency found in gastrectomized animals. This possibility is borne out by the above mentioned experiments showing that iron has some effect on the gastroprival anaemia. It is, however, not to be expected that the decrease in ripening index is caused by the iron deficiency anaemia, since such anaemias are followed by an increased ripening index (*Plum*, 1944 I—III). In order to settle this problem, a series of gastrectomized animals with pronounced gastroprival symptoms were treated with iron. The results are shown in table 2. The iron treatment has a marked effect on the iron reserves; the livers of the animals treated with iron contain 12—37 mg % iron compared with less than 6 mg % in the untreated gastrectomized animals. At the same time an increase is observed in the haemoglobin percentage. On the other hand no effect can be seen on the content of ripening principle in the blood.

It is thus seen that treatment of the anaemia with iron does not result in an increase in the ripening index, and that the two findings, the anaemia and the decrease in the reticulocyte ripening principle, occur independently of each other.

In order to further control this finding, another series of gastrectomized animals were injected with commercial liver

extract. When liver extract is given to normal animals an increase above normal is found in the ripening index. Table 3 shows that an increase is also seen in gastrectomized rats, but here the values found do not exceed normal values. No effect is observed on the haemoglobin which continues to decrease in spite of the treatment, a result which is in conformity with that of earlier investigators.

From these two series of experiments, therefore, it may be concluded that the iron deficiency and the decrease in reticulocyte ripening principle in the blood are two independent results of gastrectomy.

As already mentioned the decrease in ripening index is due to a decrease in the thermostable component of the reticulocyte ripening principle and that normal values could be restored after addition of tyrosine to the plasma. This indicates a deficiency in the tyrosine metabolism. The protein in the diet of the animals contained approximately 0.6 % tyrosine, but it seemed possible that an extra addition of tyrosine might at least partly restore normal values in the ripening principle. Table 4 shows the result of experiments with gastrectomized rats which received a diet with at least 2.6 % of tyrosine: 0.6 % bound in the proteins and 2 % free tyrosine added. After somewhat more than two months the ripening index was increased to normal in these animals. This sustains the hitherto unproven assumption that the thermostable fraction of the ripening factor in the plasma is tyrosine or perhaps a substance chemically related to tyrosine, and moreover that the tyrosine metabolism (or tyrosine resorption?) must be interfered with after gastrectomy.

A few gastrectomized rats were treated with dried stomach powder (Ventriculin "Mco"). The results of these experiments are shown in table 5. Stomach powder is obviously without effect except on the ripening index, where normal values are restored. This experiment also confirms the previous finding that the decrease in ripening index and the anaemia are two independent findings in gastrectomized rats. The effect of stomach powder is very interesting. The tyrosine content in the stomach powder is negligible and can not explain the effect, but it seems as if the stomach has some influence on the tyro-

sine resorption or on other phases of tyrosine metabolism. Further experiments are, however necessary to elucidate this problem.

Finally the reticulocytosis should be discussed briefly. The reticulocytosis can be explained either as a result of the iron deficiency anaemia or as a result of the decreased content of reticulocyte ripening factors in the blood, perhaps as a combination between both causes. The experiments given in tables 3—5 where the ripening index is brought to normal values without any influence on either the anaemia or the reticulocytosis show, however, that the decrease in ripening principle must play very little rôle in the etiology of the reticulocytosis. As seen in table 2, the percentage of the reticulocytes decreases during treatment with iron, but normal values are not nearly restored. A considerable production of red cells must, however, take place during the iron treatment which is sufficient to explain the persistent reticulocytosis during the iron treatment. Nothing speaks against the assumption that the reticulocytosis is caused by the iron deficiency anaemia.

The rats gained in weight, at least during the first three months following gastrectomy. This indicates that the food resorption in general cannot be impaired to a major degree. The findings here observed seem to be caused by a deficiency in iron resorption and/or metabolism and tyrosine metabolism and/or resorption. According to *Higgins* we may further add a deficiency of folic acid, and *Petri* and his collaborators found some improvement after addition of other components of the B-complex.

### Summary.

We found the following abnormalities in rats after gastrectomy:

- 1) a microcytic anaemia,
- 2) a reticulocytosis,
- 3) an iron deficiency,
- 4) a decreased content of reticulocyte ripening factors in the plasma.

As it is possible to improve the anaemia with iron without any influence on the ripening factors and to restore normal

Table 1. Effect of gastrectomy on blood picture, ripening<sup>1</sup>

	Initial value		25-35	
Number of observations..	10		20—26 <sup>1</sup> )	
Body weight, grams .....	188	(162—241) <sup>2</sup> )	202	(156—275)
Haemoglobin, % .....	89	(82—94)	75	(58—92)
Millions of red blood cells per mm <sup>3</sup> .....	8.9	(7.2—10.1)	9.3	(4.2—12.6)
Thousands of white blood cells per mm <sup>3</sup> .....	11	(8.8—13.9)	25	(9.8—40)
Reticulocyte % .....	0.7	(0.5—1.0)	10.0	(1.8—25.8)
Ripening index in plasma direct .....	0.82	(0.78—0.87)	0.72	(0.60—0.82)
activated with tyrosine.	0.85	(0.80—0.90)	—	—
Liver iron mg % .....	35	(30—38) <sup>3</sup> )	—	—

<sup>1</sup>) The number of observations varies: e.g. haemoglobin percentage is determined on 25 rats, ripening index only on 20.

<sup>2</sup>) average, and range of values given.

<sup>3</sup>) only two determinations.

Table 4.

Effect of 69 days treatment with 2 % tyrosine added to food of rats gastrectomized 68—106 days previously.

Rat No	G 90	G 119	G 135
Days after gastrectomy on which treatment was begun .....	106	80	68
Haemoglobin, %			
before treatment ...	62	50	49
after treatment ....	60	67	55
r. b. c. count millions per mm <sup>3</sup>			
before treatment ...	10.9 <sup>2</sup> )	9.9	8.8
after treatment ....	8.0	6.2	5.2
Reticulocytes, %			
before treatment ...	21.7	11.2	17.3
after treatment ....	28.4	26.2	32.2
Ripening index			
before treatment ...	0.66	0.64	0.63
after treatment ....	0.75 (0.79) <sup>1</sup> )	0.78 (0.84)	0.78 (0.84)
Liver iron, mg % ....	3.7	1.2	1.9

<sup>1</sup>) directly determined (after activation with tyrosine).

<sup>2</sup>) determination 64 days before beginning of treatment, corresponding haemoglobin = 77 %.

index and iron reserve in rats days after gastrectomy.

days after gastrectomy				
55-65	85-120		140-163	
17-25	12-13	4		
219 (165-300)	219 (160-285)	198	(159-275)	
65 (34-92)	60 (42-85)	40	(34-51)	
8.5 (5.2-12.2)	10.0 (8.2-14)	8.2	(6.9-8.9)	
25 (16-54)	22 (17-30)	29	(21-40)	
16.5 (2.6-26.2)	10.0 (3.6-23.4)	25	(13.6-34)	
0.67 (0.60-0.77)	0.57 (0.49-0.69)	0.56	(0.49-0.63)	
—	0.81, 0.88 <sup>5</sup> )	0.82	(0.78-0.85)	
5.9 <sup>5</sup> )	—	4.2	(3.8-4.6) <sup>6</sup> )	

<sup>4</sup>) 6 determinations.

<sup>5</sup>) Only one determination.

<sup>6</sup>) 3 determinations.

Table 5.

Effect of dried stomach powder given to gastrectomized rats for 65 days.

Rat No	G 60	G 64
Days after gastrectomy on which treatment was begun .....	101	99
Haemoglobin, %		
before treatment .....	62	85
after treatment .....	31	72
r. b. c. count millions per mm <sup>3</sup>		
before treatment .....	10.4	9.8
after treatment .....	7.5	7.7
Reticulocytes, %		
before treatment .....	15.9	4.2
after treatment .....	27.2	6.0
Ripening index		
before treatment .....	0.52 (0.82) <sup>1</sup> )	0.53
after treatment .....	0.83 (0.87)	0.80 (0.87)

<sup>1</sup>) directly determined and after activation with tyrosine.  
25 % dried hog stomach added to diet for 65 days.

Table 2.  
Effect of iron administered to gastrectomized rats.

	Rat No	G 115	G 127	G 128	G 135
Days after gastrectomy on which treatment was begun	101	90	90	83	
Haemoglobin, %					
before treatment	58	56	42	53	
after treatment	71	69	71	69	
r. b. c. count, millions per mm <sup>3</sup>					
before treatment	10.6	11.2	8.2	9.0	
after treatment	—	7.5	7.8	8.7	
Reticulocytes, %					
before treatment	9.6	16.2	23.4	16.3	
after treatment	9.1	10.2	13.0	7.1	
Ripening index					
before treatment	0.62	0.64	0.68	0.65	
after treatment	0.69 (0.84) <sup>1)</sup>	0.68 (0.81)	0.72 (0.81)	0.68 (0.81)	
Liver iron, mg %	15.8	12	22.5	37	

The injections were determined and after activation with tyrosine. The injections were given twice with an interval of one week. The animals were killed one week after the last injection.

<sup>1)</sup> directly determined and after activation with tyrosine.  
100 mg Fe was injected subcutaneously as a complex compound with ascorbic acid. The injections were given twice with an interval of one week. The animals were killed one week after the last injection.

Table 3.  
Effect of liver extract given for 67 days to gastrectomized rats.

	Rat No	G 53	G 61	G 68	G 57 Control <sup>2)</sup>
Days after gastrectomy on which treatment was begun		137	101	94	102
Haemoglobin, %					
before treatment		66	68	87	102
after treatment		66	64	72	96
r. b. c. count, millions per mm <sup>3</sup>					
before treatment		11.0	10.5	8.7	9.0
after treatment		7.9	7.4	11.4	8.4
Reticulocytes, %					
before treatment		17.0	4.3	5.7	2.5
after treatment		17.9	32.2	8.5	2.5
Ripening index					
before treatment		0.55 (0.76) <sup>1)</sup>	0.50	0.55	0.80 (0.86)
after treatment		0.81 (0.86)	0.80 (0.83)	0.86 (0.89)	0.86 (0.88)

<sup>1)</sup> directly determined and after activation with tyrosine.

<sup>2)</sup> laparatomized, but *not* gastrectomized.

The rats received 0.5 ml commercial liver extract (Hepsol fortior "Mco") subcutaneously once a week for two months, the last injection was given 24 hours before the animals were killed and the blood taken for the last examination.

values of ripening factors without any influence on the anaemia, it must be concluded that these symptoms occur independently of each other.

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## THE POSTURAL TEST

*An Adjuvant in the Examination of the Peripheral Circulation.*

By

*E. Jarlov and N. V. Jarlov.*

Since August Krogh published his world-renowned studies on the anatomy and physiology of the capillaries the interest in the peripheral circulation has been increasing markedly, not only among physiologists but also in high degree among clinicians. In their dealing with cases of gangrene, the surgeons were repeatedly faced by circulatory problems, and they were the first to carry out a number of investigations of clinical interest. In this country, *Ipsen* has given some valuable contributions to the physiology of the peripheral vessels under normal and pathological conditions in his studies concerning surgical aspects of the sympathetic nervous system. Indeed there can be no doubt that he has had an inciting influence on Danish research in the clinical aspects and pathogenesis of the vascular diseases and in the physiology of the peripheral circulation (*Christensen, Haldbo, Vanggaard, Floystrup* and others).

At the same time, investigation into these problems has also been progressing rapidly in other countries, more recently giving rise to a number of monographs, most of which have appeared independently of each other — because of the wartime isolation of the investigators (*e. g. Ratschow 1943, Abramson 1945 and 1946, Allen, Barker & Hines 1946, Richards 1946*).

The technique to be employed in such studies will naturally be associated with considerable difficulties, and the sources of errors are numerous. Therefore, a number of methods, qualitative and quantitative, have been tried out — methods based on various principles, *e. g.*, simple observation of change in color, registration of the skin temperature, different forms of pressure

measurement, oscillometry, different forms of plethysmography, gas analysis on arterial and venous blood, capillaroscopy, arteriography. Furthermore, these methods have been combined with various tests, among which particular mention is to be made of direct and indirect chilling and heating, deep respiration and respirator pauses, nerve blocking, administration of vasoconstricting and vasodilating remedies, and "pain tests".

A considerable advance in this field is to be credited to *Hertzman* and collaborators, who during world war II elaborated a sphygmographic technique based on photo-electric registration of the pulsation in the most peripheral vessels. Independently of these investigations, in this country in 1943-45 *E. Jarlov*, *K. G. Hansen*, *M. Ottesen* & *C. F. Wegener* worked out a double method, registering the pulsation of the peripheral vessels in the pulp of the fingers or in the tail of the rat, simultaneously with an electrophotometric and digitographic record taken by means of an extraordinarily fine and sensitive plethysmographic apparatus.<sup>1)</sup>

This technique has the advantage that the two methods a priori may be assumed to register non-identical though synchronous phenomena, namely: pulsation in the most peripheral pulsating vessels and the blood volume under the phases of the pulsation. A priori it seemed desirable to get this technique combined with a quick and reliable registration of the skin temperature, which therefore now is included in the technique. In collaboration with *K. G. Hansen*, moreover, *N. V. Jarlov* has further elaborated the technique to cover other points too, with a view to future investigations — e. g., introduction of different rates of speed for the light-sensitive films, simultaneous registration of several phenomena: pulsation recorded after both methods mentioned in the same finger, the skin temperature and possibly an electrocardiogram of the patient — all on the same film.

It is essential to examine the experimental subject under certain standard conditions, namely: at rest, at a constant room temperature, and all subjects in the same postures.

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<sup>1)</sup> For details of the digitographic method, the reader is referred to the original paper (cf. *References*).

Under these conditions the relation between the magnitudes of the amplitudes obtained after the two methods of registration is almost constant, and the same applies to the tests we have employed so far: direct chilling and warming of the hand, Hines & Brown's cold test, and the respiratory test, i. e., the effect of forced respiration and respiratory pause.

To this technique we recently have added a »postural test«, among other reasons, in order to elucidate the so-called "Buerger's exercises". These exercises consist in alternating elevation and lowering of the extremity affected, which are known from experience to give relief, especially to patients suffering from *thromboangiitis obliterans*, presumably because the inhibited circulation is facilitated somewhat by utilization of the gravitation — an assumption that has not yet been proved.

### *Technique.*

The apparatus consists of two oscillographs (from the Swedish transportable electrocardiograph) fitted in front of a camera from an old "Boulitte" cardiograph. This camera has the advantage that it is very easy to regulate the rate of the film, and in the camera there is room for a large amount of film. The digitograph is equipped with an amplifier, so that it is practicable directly to register the electric impulses oscillographically. The impulses from the photoelement, however, are able to move the oscillograph only on amplification by means of a 4-valve amplifier. The size of photoelement employed by E. Jarløv and collaborators was as follows: 8 cm. in diameter, 2 cm. in height — and it weighed considerably. Now it is replaced with a small photocell (a tube of  $4\frac{1}{2} \times 2$  cm.). Owing to the small size of the cell it now is practicable to apply both methods of registration to the same finger (or to the tail of a rat) at the same time.

A schematic drawing of the apparatus is shown in Fig. 1. On employment of the aforementioned sphygmographs, the records show the pulse amplitude on a constant base line. The changes in blood volume (total volume) of the finger are not registered with this "capacity-coupled" amplifier. ("This technique is equivalent to placing a leak sufficiently large in a mechanical plethysmograph to prevent changes in the base line, but not so large as to prevent adequate recording of the oscillations due to the pulse.") A "resistance-coupled" amplifier or a very sensitive string-galvanometer is required for this purpose (7—8).

The skin temperature is registered by means of a thermoelectric technique described by Vanggaard. With the apparatus de-

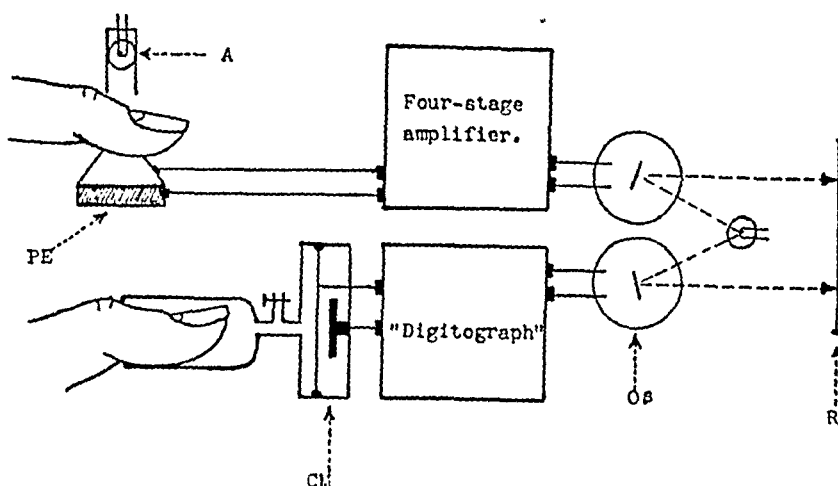


Fig. 1.

- A illumination  
 PE photoelement  
 CM condenser-microphone  
 Os oscillograph  
 R registering paper

scribed by *Vanggaard* the readings can be done 5-7 sec. after the feeler is placed on the skin.

Fig. 2 shows sphygmograms from normal adults taken at a room temperature of 21°. The two records — especially the tracings from the digitograph — are very similar to the wellknown arterial pulse curve, showing a steeply ascending limb and a more slowly descending one, corresponding to the systolic and diastolic phases.

The dicrotic wave on the descending limb is seen in both records, but there is some difference between the two — perhaps because the methods do not record identical phenomena: one gives the change in color, while the other gives the pulse wave.

As to the height of the pulse oscillations in normal adults at rest, we find more or less regular waves due to the respiration. Further, other irregular changes are seen in the height of the waves, often of longer duration. *Vanggaard* has shown that even under constant experimental conditions the skin temperature oscillates about a constant level, the variations being abrupt and transitory. This phenomenon is interpreted by Vang-

Fig. 2. P = Electrophotogram of 4. left finger. D = Digitogram of 2. left finger. (♂ 29 year. Roomtemperatur 22° C.)

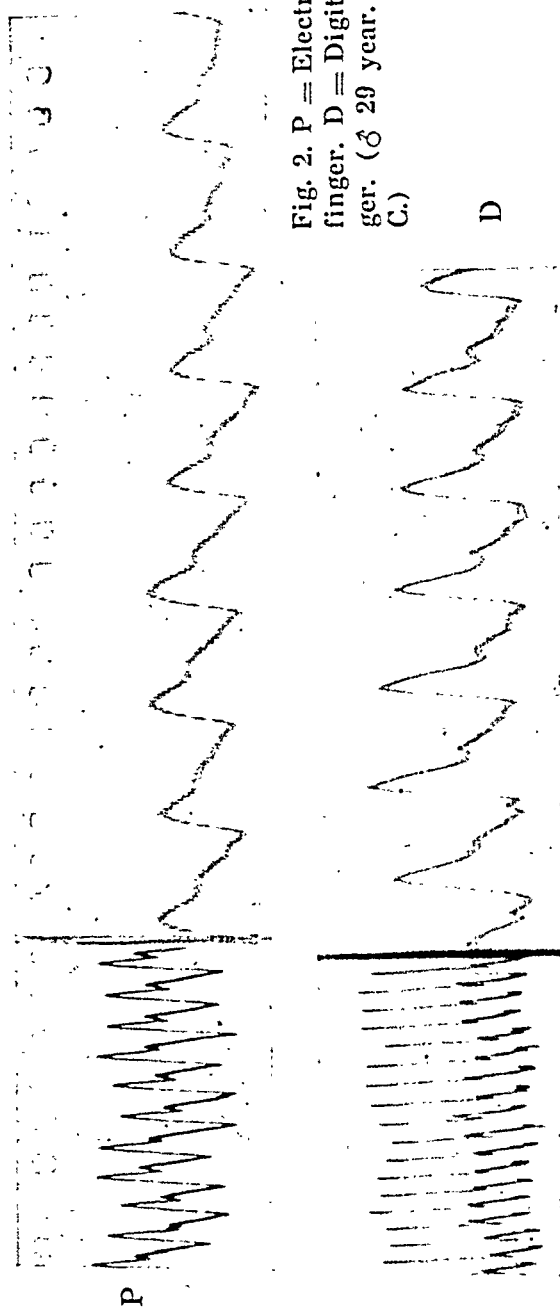
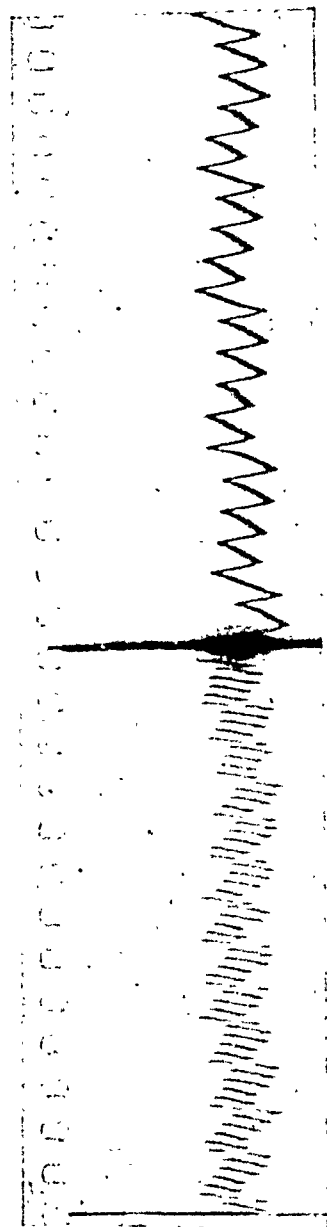


Fig. 3. "Digitogram" of a rats tail. (Roomtemperature 22° C.)



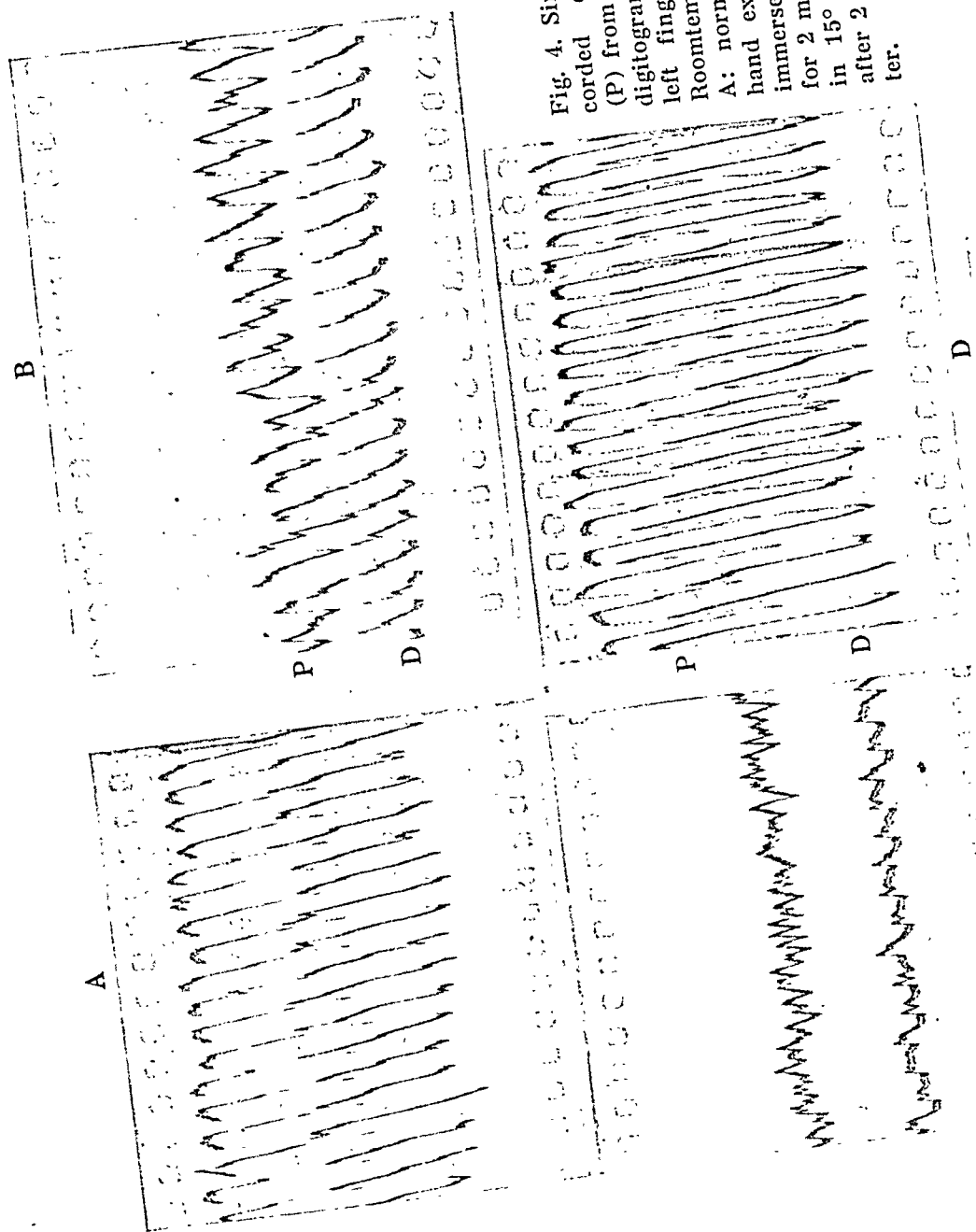


Fig. 4. Simultaneously recorded electrophotogram (P) from 4. left finger and digitogram (D) from 2. left finger. ( $\delta$  27 year. Roomtemperature 21° C.)  
 A: normal. B: after the hand examined has been immersed in 21° C. water for 2 min. C: after 2 min. in 15° C. water and D: after 2 min. in 40° C. water.

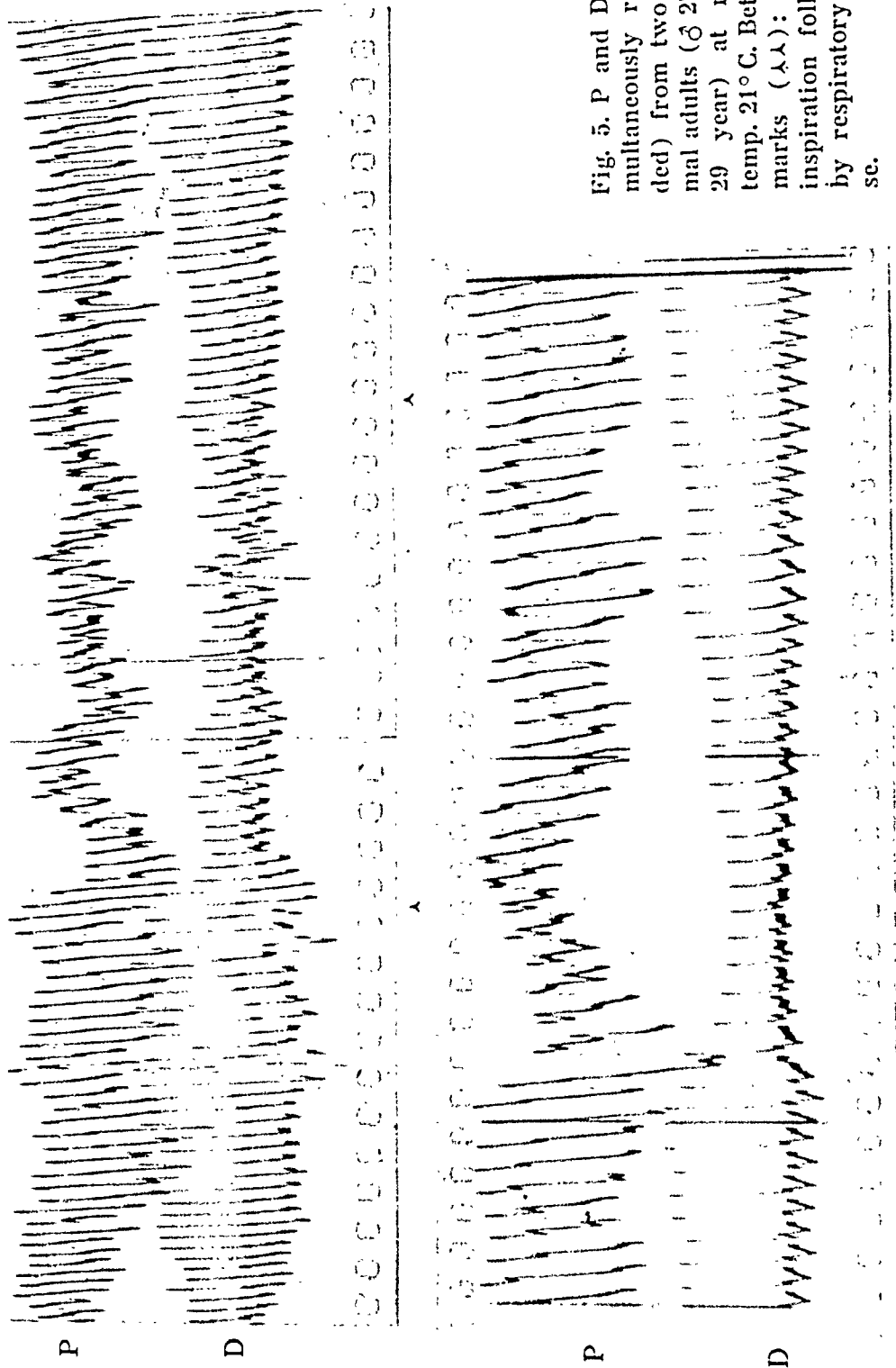
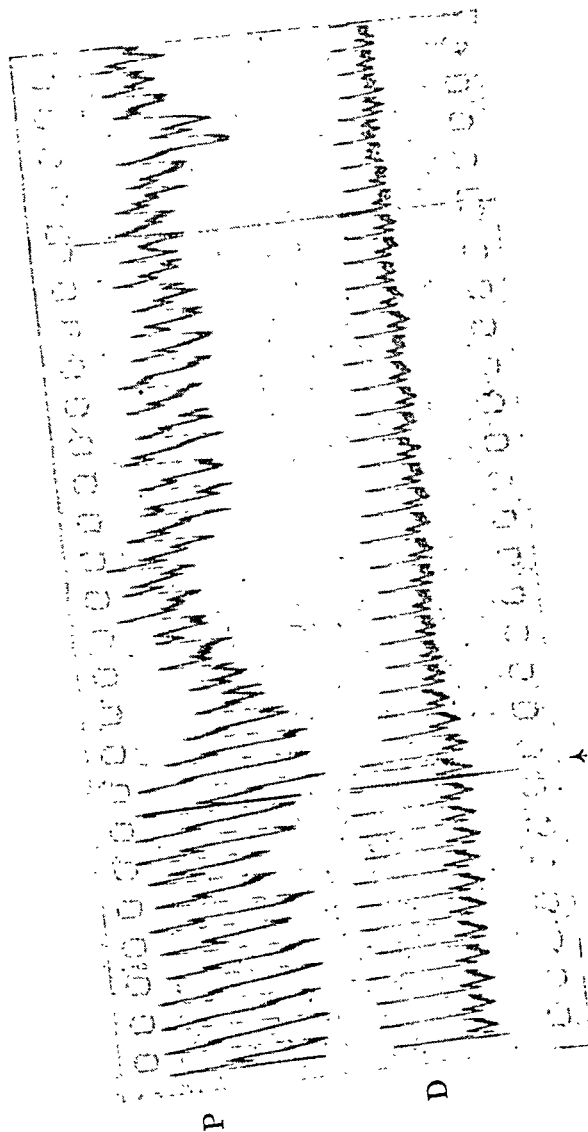


Fig. 5. P and D (simultaneously recorded) from two normal adults (♂ 27 and 29 year) at room temp. 21° C. Between marks (ΛΛ): Deep inspiration followed by respiratory pause.

Fig. 6. P and D (4. and 2. left finger recorded simultaneously) ♂ 29 year. Room temperature 22° C. At  $\lambda$  the opposite hand is immersed in icewater.



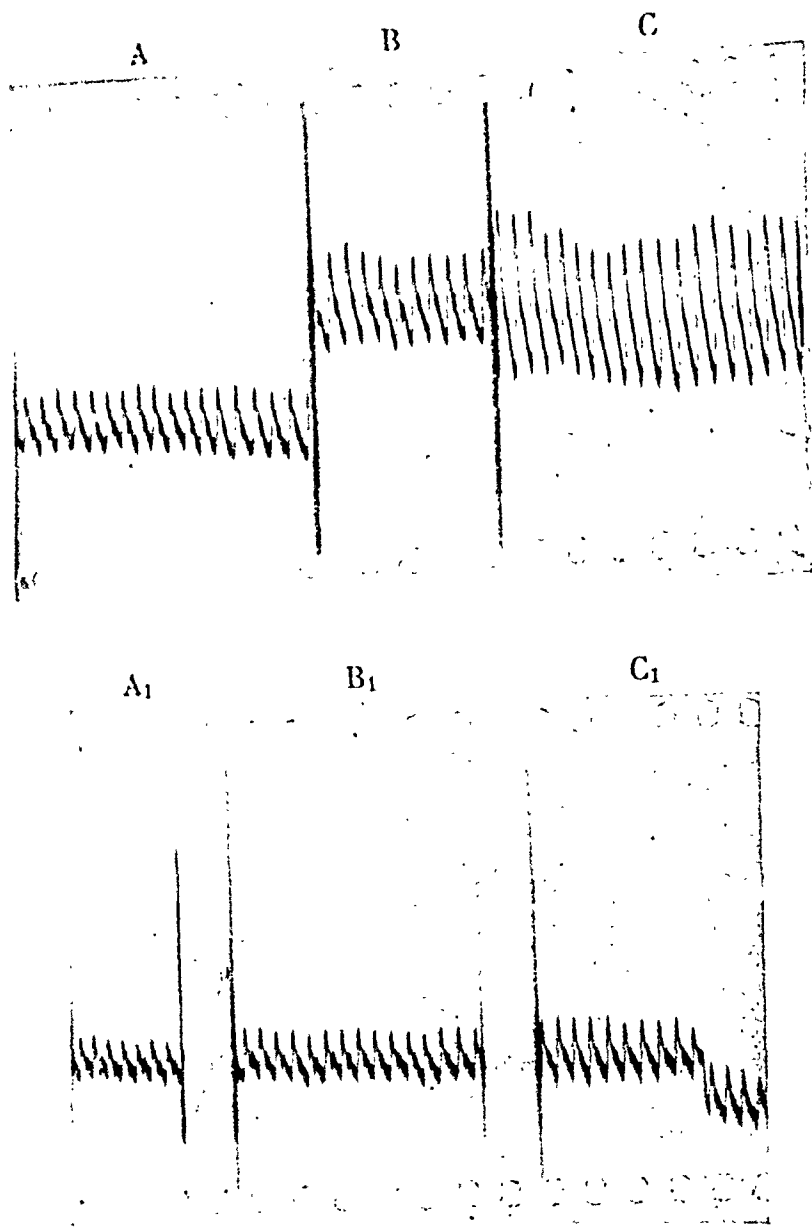


Fig. 7. Electrophotogram (P) from 2. left finger (♀ 36 year) at roomtemp. 22° C.

A: Finger placed below the level of ostium aortae.

B: — — — at — — — — —

C: — — — over — — — — —

A<sub>1</sub> B<sub>1</sub> and C<sub>1</sub>: The same posture-variations after the hand examined has been immersed in icewater for 15 sec.

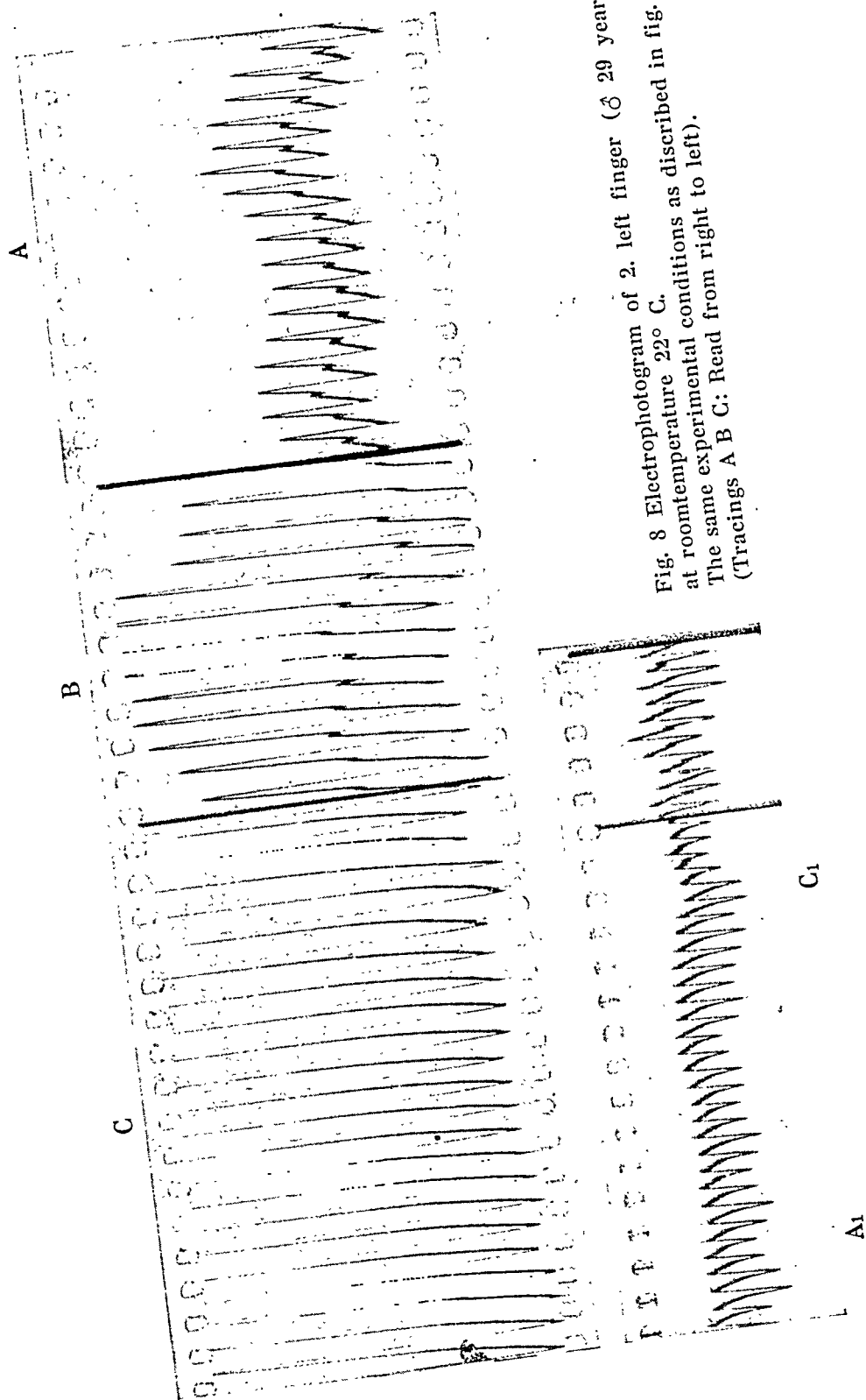


Fig. 8 Electrophotogram of 2. left finger (♂ 29 year)  
at room temperature 22° C.  
The same experimental conditions as described in fig. 6.  
(Tracings A B C: Read from right to left).

gaard as periodical alterations in the constriction of the arterio-venous anastomoses, occurring as an integral part of the heat regulation of the body. Thus, even under normal conditions the tone of the peripheral vascular system seems to vary within rather wide limits. While the tone of the vessels largely depends on the room temperature, it is also influenced by nervous and humoral conditions.

As mentioned above, the relation between the amplitudes obtained with the two methods has been fairly constant in the tests employed so far. In the "postural test", however, the matter stands rather differently. When the hand was held at different levels in relation to that of the aortic ostium, a striking difference was found in the amplitudes obtained with the two methods. The digitographic method gave only insignificant deviations resulting from the postural changes. With the photoelectric method, the amplitude was reduced by about 50 % when the hand was lowered about half a meter below the aortic level, and it was increased by 300—400 % of the initial value when the hand was raised half a meter above the aortic level. These changes take place within 2-3 sec. after the hand has been brought into the position in question.

These phenomena become most conspicuous when the hand is warm. On repetition of the postural test after the hand has been immersed in ice-water for 15-20 sec. the amplitude at the level of the aortic ostium is still found to be fairly distinct, but on the postural changes this amplitude is altered but slightly or not at all.

The large amplitudes registered after the photoelectric method in a warm elevated hand cannot be interpreted simply as an increase in the blood perfusion. For it is a well-known fact that elevation of an extremity sooner or later will give signs of ischemia — especially if the peripheral circulation is impaired already. The increased amplitude shows merely that the momentous variation in the blood content of the finger during systole and diastole is greater when the hand is elevated. The disappearance of this phenomenon after marked but brief chilling may perhaps be interpreted as follows:

When the hand is warm, most of the arteriovenous anasto-

moses are open, and a greater part of the arterial blood volume will flow directly over into the veins. On elevation of the hand the venous pressure will fall from positive to negative values, and this will greatly facilitate the venous reflux. So it seems rather likely that the most peripheral parts of the veins are able to empty more rapidly even though relatively large amounts of blood are supplied in the systole through the open arterio-venous anastomoses. The blood flow through the peripheral sections of the veins becomes somewhat "pulsating". It seems conceivable that the brief but strong chilling makes a good many anastomoses close, so that the minute volume of the finger is lowered, and the greater part of the perfusion will proceed by way of the capillaries. Owing to the increased resistance in the peripheral circulation, it is reasonable to expect the return flow to be less "pulsating", on which account we now find no large amplitudes in the electrophotogram even though the hand be elevated.

When the digitograph fails to register this phenomenon, it presumably is to be interpreted as follows: This technique registers the pulsating vessels — in other words, the "arterial" part of the function — whereas the electrophotometric method, registering the variations in the blood volume, reflects especially the venous flow. This may be decided with certainty only if we succeed in establishing which vascularized layers are penetrated by the light — probably only the most superficial. It is our hope that it will prove technically practicable to investigate this question thoroughly.

If the interpretation here advanced might prove correct, it should be possible on clinical employment of this technique in the individual cases to obtain reliable information about 1) the functional capacity of the tiniest arterial vessels, 2) the function of the tiniest venules, and 3) the function of the arterio-venous anastomoses and thus the capacity of the organism for heat regulation.

Future studies on a normal material as well as a patient material with well-established circulatory lesions will be able to confirm or invalidate this working hypothesis, which for us forms the foundation for new experiments. For the sake of

clearness, for the findings registered in the digitogram we use the term "volume variations", in the electrophotogram "color variations".

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ANTAGONISM BETWEEN SULFATHIAZOLE AND  
PTEROYLGLUTAMIC ACID ("FOLIC ACID")

By

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According to the Woods-Fildes theory for sulfonamide action *p*-aminobenzoic acid is supposed to act as an essential metabolite, a coenzyme, which may be displaced from an — for the bacteria essentially important — enzyme by sulfonamides and certain other compounds, which, like *p*-aminobenzoic acid, are *p*-substituted derivatives of aniline. Shortly after this hypothesis had been set up *p*-aminobenzoic acid (PABA) was for the first time isolated from yeast. It is not thereby proved, however, that this compound as such occurs in natural products, since a disintegration of the original, biologically active substance might have taken place during the isolation. This isolation of PABA only shows that we have to do here with a derivative of PABA not substituted in the nucleus; and the postulate of PABA itself as the essential metabolite is based chiefly on the very strong and specific activity of PABA as a sulfonamide antagonist. On the other hand PABA is a strikingly simple compound compared with other coenzymes, and it has not, like those, definitely proved to have vitamin properties for higher organisms.

By the isolation and elucidation of the constitution of pteroylglutamic acid ("folic acid") there was now found in nature a more complex derivative of PABA with vitamin properties for higher organisms, which might conceivably enter as a coenzyme into a redox enzyme, in a similar way as e.g. vitamin B<sub>2</sub>. The question then suggests itself whether this pteroylglutamic acid is not the proper coenzyme, and whether the Woods-Fildes theory should not be modified to the effect that the sulfonamides do not directly displace PABA, but interfere with the formation of pteric acid, which is probably produced from a pteridine

plus PABA, or of pteroylglutamic acid. In the presence of certain other compounds, containing, like PABA, an aromatic amino-group, a formation of derivatives of these compounds analogous to pteric acid should be possible and they would probably be biologically inactive.

If this hypothesis is correct pteroylglutamic acid should, like PABA, act as an antagonist against sulfonamides, but only where bacteria are concerned which themselves are able to synthesize pteric acid or pteroylglutamic acid. In case of bacteria requiring these substances as growth factors (*Str. faecalis* R., *Lactobacillus casei*) no such antagonism should be present, i.e. sulfonamides should have no inhibitory effect on the growth of these bacteria.

As a matter of fact Lampen and Jones<sup>1)</sup> showed that the growth of *Streptococcus faecalis* and *Lactobacillus casei* in the presence of pteric acid derivatives is inhibited only by sulfonamides in very high concentrations. Lampen and Jones concluded from these and other experiments that the primary point of sulfonamide inhibition is the interference with the synthesis of pteroylglutamic acid via PABA. In a quite recent publication<sup>2)</sup> Lampen and Jones showed that the inhibition by sulfonamides of *Lactobacillus arabinosus* and *Streptobacterium plantarum*, which require PABA, but not "folic acid", for growth is antagonized non-competitively by pteroylglutamic acid. At a certain level of this compound sulfapyridine is completely inactive.

We have investigated the effect of pteroylglutamic acid on the inhibition by sulfathiazole of the *Pneumococcus*, an organism which itself can synthesize PABA and presumably also pteroylglutamic acid.

The basal medium and general technique used in this investigation have previously been described<sup>3)</sup>. The pteroylglutamic acid used was a preparation from the Lederle Laboratories, Inc. By N-analyses (micro-Dumas) the correct nitrogen content was found: 22,33 and 21,75 % N, calculated for  $C_{10}H_{10}O_6N_7$ : 22,2 % N. The inoculum was 10–20.000 in 5 ml. Turbidity was used as criterion of growth.

The results show that in this case growth is strongly and competitively inhibited by pteroylglutamic acid.

Table 1.

Antisulfonamide Activity for *Pneumococcus* Type I (Neufeld's strain) of Pteroylglutamic Acid.

Minimal effective concentration of sulfathiazole in the presence of varying concentrations of pteroylglutamic acid.

Pteroylglutamic acid conc. $\times 10^6$ (mol/l)	Sulfathiazole conc. $\times 10^6$ (mol/l)*
100	> 800
20	400
12	200
5	100
0	25

Under the present experimental conditions a concentration of  $50.10^{-6}$  mol/l of sulfathiazole was bactericidal; growth was completely inhibited, when the concentration of sulfathiazole was  $25.10^{-6}$ . Subcultures grew well, however, and in the concentration of  $12.10^{-6}$  growth was observed after 24 hours. In the presence of PABA in the concentration of  $1.10^{-6}$  mol/l growth was not inhibited until the concentration of sulfathiazole was  $400.10^{-6}$  mol/l. This concentration of sulfathiazole required  $20.10^{-6}$  mol/l pteroylglutamic acid for neutralization. The pteroylglutamic acid thus seems to be about 20 times less active as antagonist than PABA.

Although pteroylglutamic acid thus has a strong antagonistic effect one would have expected it to be at least as great as that of PABA, if the latter should act only as a precursor of pteroylglutamic acid. Lampen and Jones observed the same low activity of pteroylglutamic acid as compared to that of PABA in supporting the growth of *Lactobacillus arabinosus*. They offer three possible explanations to this phenomenon. Further data are necessary to settle the question. We should, however, like to suggest a fourth, more general explanation: While sulfathiazole and other sulfonamides may interfere with the formation of pteroylglutamic acid, the compounds produced from the sulfonamides may interfere with the function of pteroylglutamic acid as a coenzyme. Accordingly there are two displacement reactions to be considered, viz. the competition between PABA and

\*) Turbidity readings after 24 hrs. Inhibition still after 48 hrs. requires concentrations 1.5 to 2 times greater.

the sulfonamide for the pteridine and the competition between pteroylglutamic acid and the hypothetical sulfonamide-pteridine for the apoenzyme. Provided the affinity of PABA to the pteridine is considerably greater than that of the sulfonamide, while pteroylglutamic acid and the sulfonamide-pteridine do not differ essentially in their affinities to the apoenzyme, we have an explanation to the low antagonistic activity of pteroylglutamic acid as compared with that of PABA.

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## PHAGOCYTIC ACTIVITIES OF VARIOUS TYPES OF LEUCOCYTES\*)

By

*M. Jersild, M. D.*

Those who have studied phagocytosis, for example as immune reaction in various diseases, will have observed that almost all the polynuclear leucocytes ingest equal numbers of bacteria whenever the phagocytic activity is at all lively. There are certain exceptions, however: the eosinophil leucocytes, which generally are lacking in phagocytic activity. On the other hand, there seems to be no conspicuous difference in degree of phagocytosis between the unsegmented and the segmented neutrophils. The monocytes always ingest actively, whereas the lymphocytes, large and small, exhibit no power of phagocytosis.

A question which naturally suggests itself is to what extent more immature types of leucocytes not occurring in normal blood are capable of ingesting bacteria, and whether, on the basis of its phagocytic activity, a leucocyte can be classified as belonging to the myeloid system or the lymphatic system.

Phagocytosis research with the aid of blood from patients with various forms of leukemia has been reported on in the literature, but in no more than a few communications in which the results did not agree.

*Jacobsthal* in 1921 examined the phagocytic activity of the myeloblasts in a case of acute myeloblastleukemia, and the myelocytes in chronic myeloid leukemia, his test material being particles of cinnabar. The myeloblasts showed lively phagocytosis, whereas the myelocytes from a case of chronic leucosis engulfed only few of the particles. Eosinophil cells from a pat-

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\*) This study was supported by a grant from the Anders Hasselbalch Anti-Leucemia Foundation.

ient with Hodgkins' disease showed no phagocytosis of cinnabar particles, but lively activity against tubercle bacilli.

In 1937 *Strumia* and *Boerner* in their experiments on phagocytosis used either leucocytes isolated by centrifuging citrated blood, or heparinized blood in which the leucocytes were not separated from the erythrocytes. Both procedures gave uniform results. The bacteria used were pneumocci and *Staphylococcus albus* or *aureus*. These authors tested the phagocystic activity of the leucocytes from patients with various forms of leukemia:

Lymphocytes from lymphatic leukemia, acute as well as chronic, showed no phagocytic powers at all. In the case of normal blood the lymphocytes also remained inactive.

On testing the cells of several patients with myeloid leukemia the authors observed marked phagocytosis in the neutrophil polynuclear cells and metamyelocytes, less in myelocytes and promyelocytes; younger myeloid cells showed only doubtful phagocytosis.

The cells from a case of acute monoblastic leukemia showed active phagocytosis, whereas those from mononucleosis infectiosa were inactive.

Eosinophil cells showed little or no phagocytosis.

In 1938 *Tanabe* studied phagocytosis in various cases of leukemia by observing the power of the cells to engulf Indian-ink particles. He found that lymphocytes and basophil leucocytes had no such power, eosinophil cells only little, whereas monocytes were actively phagocytic. In myeloid leukemia he observed phagocytosis in myeloblasts when the disease was sufficiently far advanced, whereas he considered that the activity subsided in the agonal stage. In acute myeloblastic leukemia he was unable to observe phagocytosis in the immature cells.

*Herzog* (1938) experimented with heparinised blood and added *Staphylococcus aureus* or *Streptococcus viridans*. This author's observations differ considerably from the above: In lymphatic leukemia he sometimes found phagocytosis in the case of large lymphocytes rich in protoplasm. He found marked phagocytosis in only one small, mature lymphocyte.

In all cases of mononucleosis infectiosa (3 patients) he found pronounced phagocytosis in the mononuclear cells.

In myeloid leukemia he observed a phagocytosis which was

directly proportional to the degree of maturity of the cells (from polynuclears decreasing rapidly to myeloblasts). Of immature cells the only ones to show pronounced phagocytosis were histoid stem cells and monoblasts from a case of leukemic reticulosis.

Huddleson & Munger (1936) tested marrow blood from guinea-pigs immunized with *Bacillus abortus* Bang, as well as blood from a patient with myeloid leukemia. To the latter they added immune serum from a patient with undulant fever. Phagocytosis was tested against *Bac. abortus* Bang.

The marrow blood was found to contain only very few phagocytic cells younger than metamyelocytes, and in the leukemic blood there were no phagocytic cells younger than metamyelocytes.

It is evident from the various investigations that there is some divergency in the results, attributable perhaps to the great differences in experimental technique. There is one possibility, however, which must be taken into consideration: insufficient histological differentiation between the various forms of cells. It is nothing uncommon for even experienced hematologists to have to give up where it is a question of determining the genesis of a mononuclear cell, and for investigators to compromise on the term »stem cell leukemia« where differentiation is impossible.

### *Own Investigations.*

#### *Technique.*

In the phagocytic reaction the technique already described by the author (*M. Jersild*) has been employed with certain modifications:

About 2 c. c. of the patient's blood are transferred by venous puncture to a thick-walled, small test tube. The blood is defibrinated by vigorous shaking with two small glass balls for eight minutes, whereafter the activity of the leucocytes can be examined without the addition of anticoagulants, which are shown by experience to reduce this activity. If the blood samples are tested within six hours after being taken — and especially if they have been stored in a cool place — the activity of the leucocytes will be found to be unchanged.

The blood is tested against a suspension of *Bac. abortus* Bang in

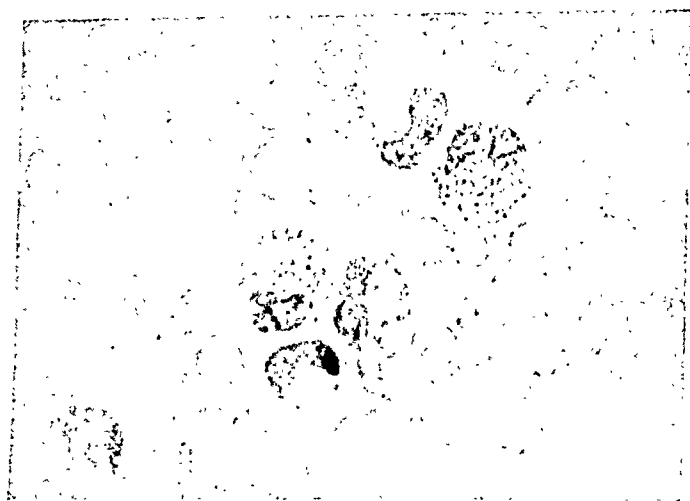


Fig. 1. Phagocytosis in myeloid leucemia.

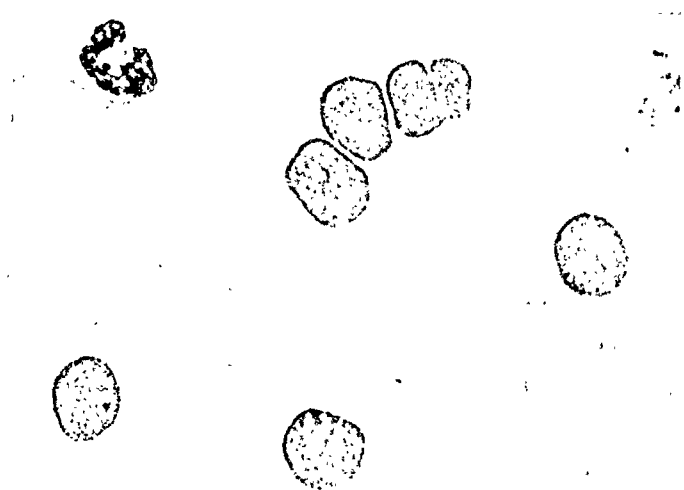


Fig. 2. Case 2, Giemsa stain.

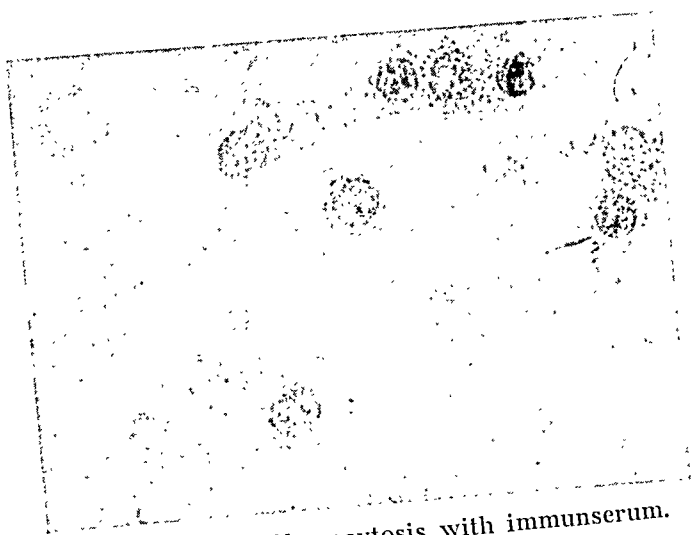


Fig. 3. Case 2. Phagocytosis with immunserum.

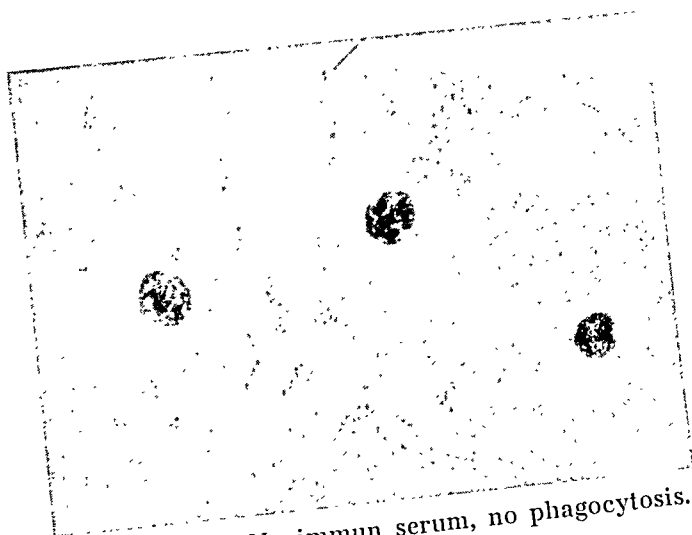


Fig. 3. Case 2. No immun serum, no phagocytosis.

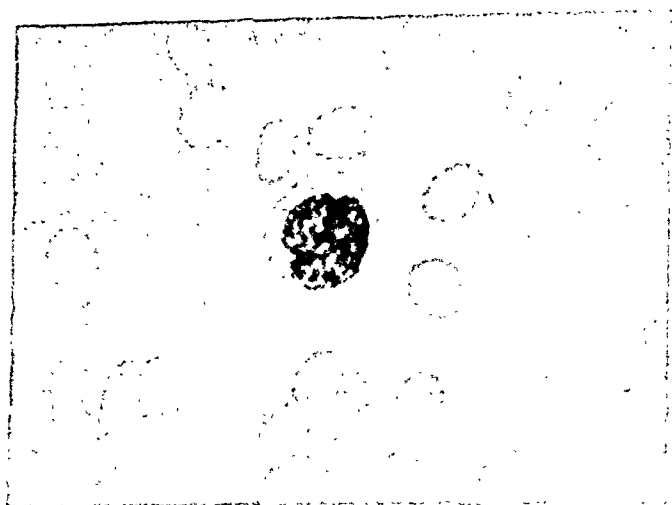


Fig. 5. Case 3. Giemsa stain.

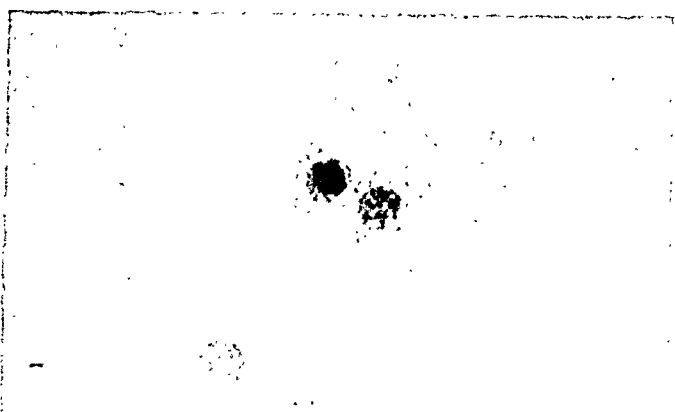


Fig. 6. Case 3. Phagocytosis.

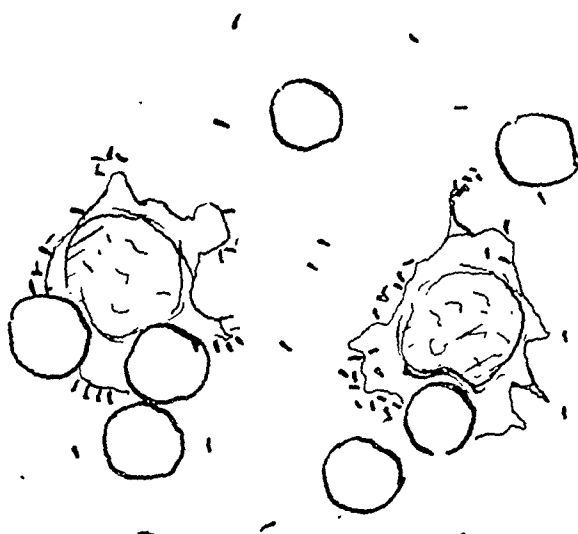


Fig. 7. Case 3. Motility during phagocytosis.

saline (density as 1 cm. by the *Gates* apparatus, i. e. a bent-over platinum loop when lowered into the suspension disappears 1 cm. below the surface, seen through the mouth of the tube). Of this suspension 0.1 c. c. is transferred to a tube into which has been pipetted 0.002 c. c. (i. e. 0.02 c. c. of serum diluted 1:10) of a serum agglutinating *Bac. abortus* Bang in a dilution of 1:1000. To this mixture is then added 0.1 c. c. of the defibrinated patient blood in which the leucocytes are to be examined. The tube is shaken and allowed to stand for half an hour in a waterbath at 37 ° C., during which time it is shaken again three or four times.

A drop is then spread on a clean (non-greasy) slide. (To ensure the even distribution of the leucocytes it is important that the slide used for spreading the drop is held almost at right angles to the slide on which the drop lies, as the viscosity of the mixture is lower than that of ordinary ear blood.). The slide is air-dried, hardened for two minutes in a saturated sublimate solution, washed thoroughly with water and stained with aqueous methylene blue solution 0.2 % for 10 minutes, then briefly rinsed in water.

By this method the bacteria are stained, but not the cell granules, so that phagocytosis is distinctly observable with the aid of an immersion lens. A polynuclear leucocyte will usually show maximum phagocytosis, i. e. that it has ingested more than 40 bacteria. When judging the phagocytosis of pathological forms of cells, one should always observe the phagocytosis of a few polynuclear cells as controls to ensure that the cells have retained their natural activity.

Besides the slide with the anti-*abortus* Bang serum the following experiments included control slides without this addition as well as a slide from ear blood stained with peroxydase (*Sato-Sekiya's* reaction, also known as the *Tohoku pediatric method*).

The above phagocytosis technique can be simplified somewhat by using an enterococcus strain, which can be ingested without immune serum, instead of *Bac. abortus* Bang.

### *Experimental Results:*

*Marrow blood* taken by sternal puncture from a normal person showed that no cell younger than metamyelocytes was capable of phagocytosis.

In three patients with *chronic myeloid leucosis* the same result was observed when testing peripheral blood (fig. 1): phago-

cytosis was only exceptional among cells younger than metamyelocytes (of myelocytes and younger forms only about 5% showed phagocytosis, of metamyelocytes about 30 %, of polynuclear leucocytes 100 %. Of the white blood corpuscles 96 % were peroxidase positive).

*Infectious mononucleosis:* Two patients were tested; in neither case did the mononuclear cells exhibit phagocytic activity.

*Myelomatosis:* One patient was tested from sternal puncture. The plasma cells from the marrow blood showed no phagocytosis.

*Chronic lymphatic leukemia:* The peripheral blood of seven patients was tested. In no case was there phagocytosis by the mononuclear lymphatic cells.

*Acute myeloblastic leukemia:* One patient tested. The mononuclear cells showed no phagocytosis, though 21 % were peroxidase positive.

*Case report No. 1.* Woman, 29 years, (E. W.) died after two month's highly febrile affection. Hemoglobin 47 %, red blood corpuscles 2.2 million. Leucocytes 63,200. Platelets 154,000. Differential count: almost exclusively fairly large mononuclear cells with a slightly indented nucleus with several vacuoles and angranulated protoplasm. Post mortem: Moderate enlargement of almost all lymph glands and spleen. Microscopic diagnosis: Leukemia myelogenes.

*Non-leukemic myeloid splenomegaly with leukemoid (lymphatic?) reaction.* Two patients, both with preponderantly lymphocytoid, peroxidase-negative cells in the peripheral blood. These cells exhibited marked phagocytosis:

*Case report No. 2.* Woman, 58 years (C. C.). Ill for six years with a greatly enlarged spleen but no enlarged peripheral lymph glands. At the onset there were 8000 white blood corpuscles per c.mm., at death 38,000, almost all large mononuclear cells with a leptochromatic nucleus generally indented and with several vacuoles. The protoplasm narrow, slightly basophil without granules. (Fig. 2). Hemoglobin 35 %. Red blood corpuscles 1.3 million. Platelets 15,000. Wassermann negative. Numerous ecchymoses on the skin. Received X-ray treatment in periods. Under increasing marasmus the patient died after six years' illness.

Autopsy: Spleen considerably enlarged (weight 1925 g.). Lymph glands in the mesentery slightly swollen and hyperemic.

Microscopic examination (Dr. Harald Gormsen):

Bone marrow (from femur): the marrow contains almost the maximum of cells; isolated or in small groups fat cells are seen only here and there. There is a very marked but not diffuse infiltration of the marrow by mononuclear cells of a type like small and medium-sized lymphocytes, lying in large islands or broad striae, with a number of marrow cells between. Here and there are broad streaks of maximally hyperplastic marrow without infiltration by mononuclear cells but with a distinct preponderance of young granulocytes. Rather numerous megacariocytes.

Spleen: The follicular structure is preserved almost everywhere, but the follicles are not sharply delimited from the pulpa tissue, which is not particularly rich in cells. It is fairly well filled with blood, here and there showing fibrotic changes with some reticulum proliferation. Mononuclear cells of a type like small and medium lymphocytes dominate in the red pulpa, and there are some myelo- and metamyelocytes as well as a few leucocytes, both neutrophil and eosinophil, few erythroblasts and moderate amounts of megacariocytes.

Lymph gland: The tissue structure somewhat disturbed by diffuse, fairly fresh hemorrhages, but it can be seen that the follicular structure is preserved. Among the lymphocytes are moderate numbers of immature granulocytes, especially myelocytes, few erythroblasts and isolated megacariocytes.

Liver tissue: Everywhere in the capillaries a number of mononuclear cells of the type described above, some few immature and isolated mature granulocytes, as well as a few erythroblasts. In the portal vein spaces are small infiltrates of the same cells. No megacariocytes. Liver tissue normal.

Kidney tissue: In the vessels are considerable quantities of mononuclear cells of the above-described type. No interstitial infiltrates anywhere, especially no sign of medullary haemopoiesis. Apart from a few scattered hyaline glomeruli the renal tissue shows nothing abnormal.

Conclusion: There can scarcely be a question of any form of leukemia. The histological changes, especially in the spleen, argue mostly for non-leukemic myeloid splenomegaly, which undoubtedly caused splenogenic inhibition of the bone marrow and a leukemoid (lymphatic?) reaction.

Phagocytosis: All the mononuclear cells showed very active phagocytosis, the bacteria surrounding each cell in a wide border. (Fig. 3). The control slide without immune serum showed no phagocytosis. (Fig. 4). All the mononuclear cells of this patient were peroxydase negative.

*Case report No. 3.* Woman, 70 years (A.R.). For five years had repeated characteristic attacks of gall stone. For a month had been tired and had lost weight. Temperature normal. Spleen much enlarged, extending to the crista ilei; no enlargement of the peripheral lymphglands. Leucocytes: 12,500. Differential count: Segment-nuclear leucocytes 9 %, unsegmented 3 %, monocytes 1 %, mononuclear cells of lymphocyte type 87 %. The latter cells were fairly uniformly large, the nucleus leptochromatic with fine, diffuse structure, only rarely with vacuoles, often indented (Fig. 5). The protoplasm slightly basophil without granules. Hemoglobin 26 %, erythrocytes 1.2 million. Platelets 70,000. Sedimentation rate 130 mm. Formol-gel reaction negative. Wassermann negative.

*Autopsy:* Signs of cholecystitis, cholelithiasis and pericholecystitis with abscess formation.

Spleen considerably enlarged, cut surface of natural colour with increased connective-tissue markings.

Lymph glands: Only those in the porta hepatis enlarged.

Microscopic examination (Dr. Harald Gormsen):

Bone marrow (from sternum and femur): the marrow contains almost the maximum cells; an isolated fat cell seen only here and there. Very considerable infiltration of the marrow with mononuclear cells similar in type to small and medium lymphocytes. These cells lie in broad, massive striae consisting exclusively of the mononuclear cells. Side by side with these striae are 1) marrow areas showing more or less pronounced diffuse infiltration with mononuclear cells among normal marrow cells, 2) areas with maximally hyperplastic marrow with increased granulopoiesis (myelocytes dominating) as well as fairly active erythropoiesis. Rather abundant numbers of megacariocytes.

Splenic tissue: Diffuse pulpa fibrosis many places, and fibrotic striae poor in cells as well as small hyalinised islands frequently seen in the red pulpa. The trabeculae somewhat thickened, and there is marked fibrosis around several central arteries. The follicular structure is preserved in most places. The red pulpa very rich in cells, containing especially small and medium lymphocytes, but also rather considerable numbers of immature granulocytes, especially myelocytes, few erythroblasts and moderate numbers of megacariocytes.

Lymph gland: Slight fibrotic changes, the normal structure preserved. Slight hemopoiesis, especially myelopoiesis. No megacariocytes. Many leucocytes and histiocytes in the sinusoids.

Liver tissue: In the capillaries sporadic mononuclear cells, mostly resembling lymphocytes, and scattered, immature granulocytes and erythroblasts. In the portal vein spaces very slight infiltration with the same types of cells. No megacariocytes.

**Kidney tissue:** Many mononuclear lymphocyte-like cells in the vessels. Some small interstitial infiltrates of lymphocytes around hyaline glomeruli, but otherwise no interstitial infiltration. No sign of hemopoiesis.

**Conclusion:** The question of leukemia can scarcely arise. Most probably it seems to be a non-leukemic myeloid splenomegaly with leukemoid (lymphatic?) reaction. The sclerotic changes in the spleen are of the type of the Banti spleen.

**Phagocytosis:** 66 % of the mononuclear cells showed pronounced phagocytosis (Fig. 6), whereas 96 % were peroxydase negative. By direct microscopy of the living cells on agar plates (ad modum *Oerskov*) most of the mononuclear cells showed lively motility during phagocytosis, it being possible to see how they extended pseudopodiae to all sides (see drawing fig. 7).

These investigations show that mononuclear cells only exceptionally display phagocytic activity. Consequently, this activity cannot be employed for distinguishing myeloblasts from lymphoblasts. Peroxydase-positive cells are not necessarily phagocytic, as was shown by the experiment with blood from a patient with acute myeloblastic leukemia. Marked phagocytosis was observed exceptionally in immature mononuclear peroxydase-negative cells. Both patients from whom these cells came had splenomegaly, but there was no entcargement of the peripheral lymph glands. The microscopic diagnosis was: non-leukemic myeloid splenomegaly with leukemoid reaction. (With. Bukh, Hickling).

It is possible that in phagocytosis we have a biological reaction suitable for use in differentiating the cells in this disease and thereby showing that genetically they differ from the cells in lymphatic or myeloid leukemia.

### *Summary.*

The author describes a technique whereby the phagocytic power of various forms of leucocytes against *Bacillus abortus* Bang in the presence of immune serum can be tested. Enterococci can also be employed without immune serum. Myeloid cells younger than metamyelocytes are rarely phagocytic. Lymphocytes or their pre-stages are not phagocytic. Mononuclear cells from two patients with non-leukemic myeloid splenome-

galy displayed active phagocytosis, even when peroxydase negative. The possibility of using phagocytosis as a biological test in this disease is ventilated.

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## THE EFFECT OF SODIUM IODIDE COMPARED WITH THAT OF DIIDO-TYROSINE ON THE THYROID GLAND

By

K. Kjerulf-Jensen.

The preoperative treatment of Graves' disease is still based mainly on administration of iodine in some form or other. Methylthiouracil (2-thio-4-methyl-uracil) or related compounds are, indeed, likewise used preoperatively, but not to the same extent as iodine. The treatment originally instituted by *Plummer* consisted in administration of iodine plus potassium iodide in the form of Lugol's solution. Later on *Abelin* introduced diiodotyrosine, because he observed it to have a repressing effect on hyperthyroidism caused by feeding with thyroid substance. No such effect has been demonstrated by other writers, however. Some of these writers found that diiodotyrosine had a prompter and more certain effect than sodium iodide when used preoperatively. The final effect on the hyperthyroidism is, however, the same, as pointed out by *J. Hertz*. In animal experiments potassium iodide seems to have a prompter effect than diiodotyrosine. Such experiments were carried out on guinea-pigs by *M. Krogh & Okkels* in 1937. The animals were made hyperthyroid by injection of anterior pituitary extracts containing thyrotropic hormone. Administered in adequate doses potassium iodide could more promptly than diiodotyrosine reduce the elicited rise in basal metabolism and bring about accumulation of colloid with flattening of the glandular epithelium of the thyroid.

Inhibition of the thyroxine production with a compensatory, additional production of thyrotropic hormone can be brought about by administration of methylthiouracil. This process will result in a histologically hyperactive thyroid poor in colloid. The iodine may, however, even under these abnormal con-

ditions preserve its specific power of eliciting accumulation of colloid substance, *Kjerulf-Jensen*, 1946. There is, by the way, still some doubt as to whether iodine has a direct effect on the thyroid or whether the pituitary body is the primarily influenced organ. *Astwood* (1946) has shown that iodine deficiency has a highly intensifying influence on the goitrogenic effect of small doses of thiouracil. This accords well with the hypothesis advanced by *Campbell*, *Landgrebe*, and *Morgans* that thiouracil inhibits the synthesis of thyroxine by fixing the free iodine and thus preventing the iodination of tyrosine during the synthesis.

The author has made some experiments on rats, the results of which are recorded in the present article. A comparison has been drawn between the amounts of colloid substance accumulated after administration of adequate doses of sodium iodide and diiodotyrosine respectively in connection with methylthiouracil. Administration of methylthiouracil will cause a decrease in the amount of colloid substance and the iodine content of the thyroid, as well as a cellular hyperplasia tending to counteract the decrease of the basal metabolic rate.

### *Principle of Procedure.*

The experiments were carried out on young, normal rats of both sexes, weighing from 90 to 160 gm. Previous to and during each experiment the animals were kept on a standard diet sufficient in every respect. Such doses were applied of sodium iodide, diiodotyrosine, and methylthiouracil respectively that the effect of each dose was submaximal. During the experiment itself methylthiouracil (2-thio-4-methyl-uracil), 2 mg. per 10 gm. diet, was added together with either sodium iodide or diiodotyrosine in such quantities that the iodine content was the same in 2 parallel experimental series; e. g. 0.2 mg. sodium iodide or 0.29 mg. diiodotyrosine per 10 gm. diet, or in another series 0.4 mg. sodium iodide or 0.59 mg. diiodotyrosine per 10 gm. diet. (A rat will eat about 10 gm. per 100 gm. body weight of the diet applied). Each experimental period extended over 10 days. At the end of this period the rats were killed, the thyroids

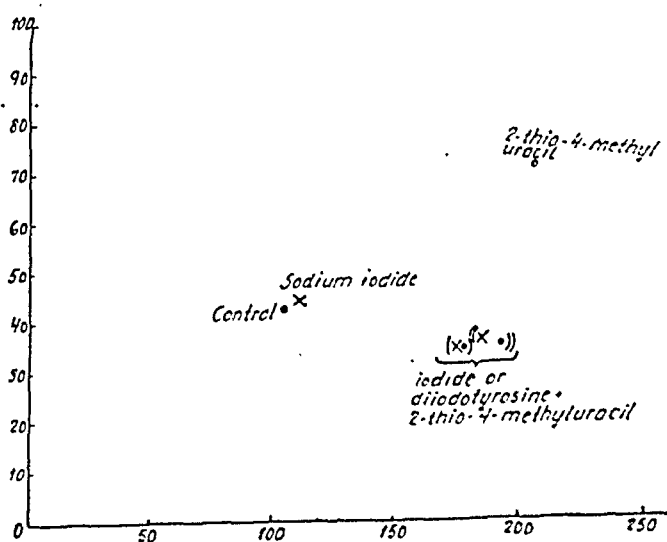


Fig. 1. Proportion of percentage contents of colloid substance to that of parenchyma (glandular epithelium plus vascular connective tissue) in the thyroids of rats given daily doses of sodium iodide, sodium iodide plus methylthiouracil (2-thio-4-methyl-uracil), diiodotyrosine plus methylthiouracil, or methylthiouracil alone.

Ordinate: parenchyma in per cent.

Abscissa: weight of thyroid in per cent of the normal calculated on the basis of the body weight.

- 10 control rats.
- × 10 rats given daily doses of 0.2 mg. sodium iodide per 10 gm. diet for 10 days.
- 10 rats given daily doses of 2 mg. methylthiouracil per 10 gm. diet for 10 days.
- (×) 15 rats given daily doses of 0.2 mg. sodium iodide plus 2 mg. methylthiouracil per 10 gm. diet for 10 days.
- (●) 15 rats given daily doses of 0.29 mg. diiodotyrosine plus 2 mg. methylthiouracil per 10 gm. diet for 10 days.
- (×) 15 rats given daily doses of 0.4 mg. sodium iodide plus 2 mg. methylthiouracil per 10 gm. diet for 10 days.
- (●) 15 rats given daily doses of 0.59 mg. diiodotyrosine plus 2 mg. methylthiouracil per 10 gm. diet for 10 days.

The points represent the average values. The spreading appears from the points in Figs. 1 a and 3.

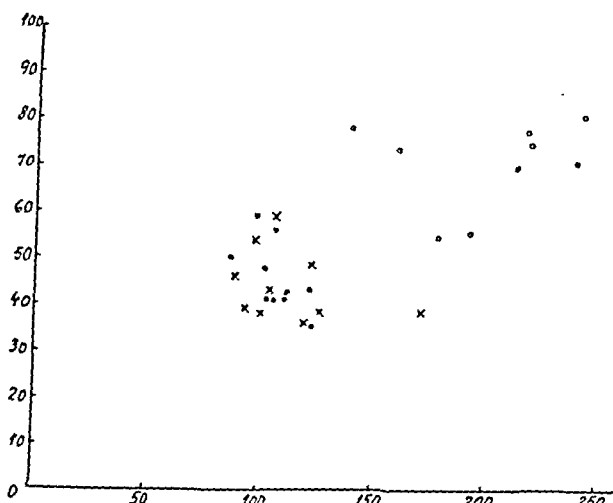


Fig. 1 a. Detailed results of the experiments with administration of sodium iodide or methylthiouracil alone, the average values of which are indicated in Fig. 1.

dissected free, hardened in formol solution, weighed, and prepared as for an ordinary histologic examination. The weight of the removed thyroid was given in per cent of the normal on the basis of the body weight, as indicated by *K. A. Jensen and Kjerulf-Jensen, 1944*. The weight of the normal thyroid was in practice expressed as  $(10 + (\text{body weight in gm.} - 60) 0.1 \text{ mgm.})$ . The proportion of the amount of colloid substance to that of parenchyma (gland cells plus vascular connective tissue) was determined by photomicrography<sup>1)</sup> of equally thick histologic preparations of the gland. The area seen in the photomicrograph to be colloid could then be cut off, after which the percentage amount of glandular epithelium was determined by weighing. Since vessels and connective tissue remain fairly unchanged during the development of goitre, this method is fit for a rather accurate estimation of the proportion of cell mass to colloid substance.

### Results.

The percentage amount of colloid substance was practically the same in normal rats and in rats which had been living under the same conditions, except that they had received an addition of

<sup>1)</sup> The photomicrographs were taken by *E. Lange, Copenhagen*.

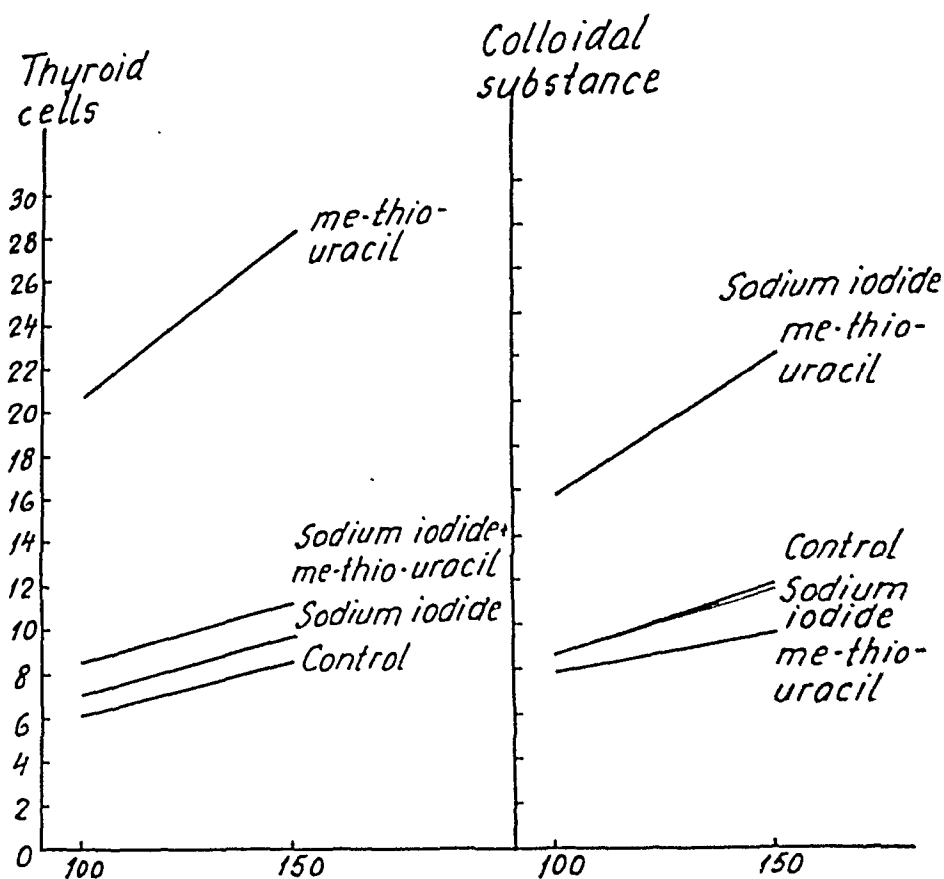


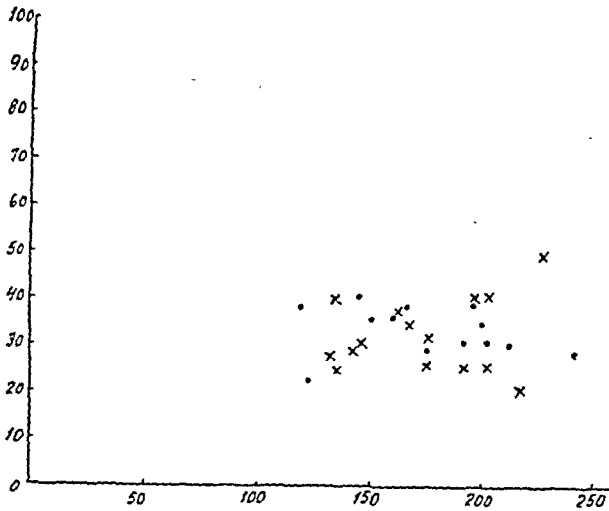
Fig. 2. Amount of parenchyma, or colloidal substance in the thyroids of rats after 10 days of administration of sodium iodide, methylthiouracil, or sodium iodide plus methylthiouracil, in amounts as indicated in Fig. 1 per 10 gm. diet.

Ordinate: mg. parenchyma or colloidal substance in the thyroid.

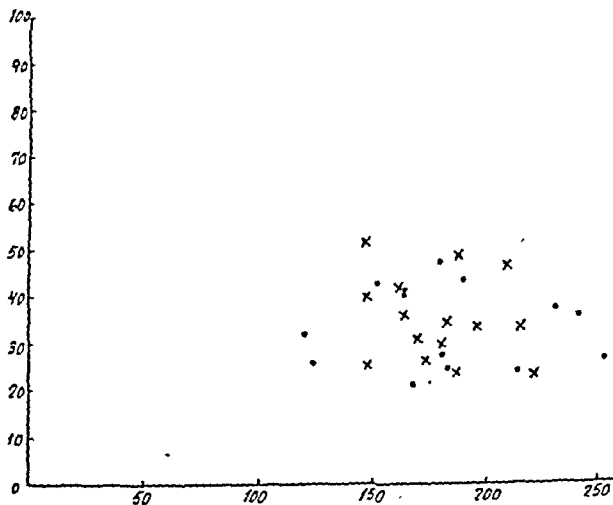
Abscissa: body weight of rats.

The oblique lines result from calculations of the contents of colloid or parenchyma on the basis of the average results from the experiments rendered in Fig. 1.

0.2 mg. sodium iodide per 10 gm. diet for 10 days (Fig. 1). The amount of parenchyma seemed reduced, if anything. Addition of a suitable, submaximal dose of methylthiouracil, on the other hand, consisting in 2 mg. 2-thio-4-methyl-uracil per 10 gm. diet brought about a considerable reduction in the percentage contents of parenchyma of the thyroid under the cellular hyperplasia. Larger amounts of methylthiouracil would add comparatively little to the effect.



*Fig. 3.* Detailed results of the experiments indicated in Fig. 1. Proportion of percentage contents of colloid substance to that of parenchyma in the thyroids of 4 groups of rats, each comprising 15 animals, after 10 days of administration of  
 x 0.2 mg. sodium iodide plus 2 mg. methylthiouracil  
 . 0.29 mg. diiodotyrosine plus 2 mg. methylthiouracil.



x 0.4 mg. sodium iodide plus 2 mg. methylthiouracil.  
 . 0.59 mg. diiodotyrosine plus 2 mg. methylthiouracil.

As appears from Fig. 2, the absolute amount of colloid substance in the entire gland remains rather unchanged during administration of methylthiouracil. This means that the growth

of the gland is due exclusively to the hypertrophy of the parenchyma, in this case 235 %, i. e. the hypertrophy is purely cellular.

If sodium iodide or diiodotyrosine is added together with methylthiouracil in doses that are equivalent with regard to iodine the cellular hyperplasia will be repressed, since the percentage parenchyma content will be considerably reduced (Fig. 1), while the absolute parenchyma content will remain nearly unchanged (Fig. 2). This means that under simultaneous administration of methylthiouracil and iodine the hyperplasia of the thyroid is due chiefly to a percentage and an absolute increase in the amount of colloid substance.

Under these circumstances diiodotyrosine proved to have the same power as sodium iodide of increasing the amount of colloid substance in the thyroid, when the two substances were applied in doses that were equivalent with regard to iodine (Figs. 4 and 5). Thus diiodotyrosine has not in these experiments been observed to have any effect on the thyroid which could not be obtained with sodium iodide alone.

These experiments seem, in other words, to show that iodine, whether in the form of sodium iodide or diiodotyrosine, represses the cellular hyperplasia elicited by methylthiouracil, when administered in suitable doses. The increased supply of iodine gives rise to an added accumulation of colloid, despite the simultaneous methylthiouracil effect.

### *Summary.*

A comparison has been drawn between the absolute and the relative contents of colloid substance and parenchyma respectively in the thyroids of rats after peroral administration of 2-thio-4-methyl-uracil, sodium iodide, sodium iodide plus methylthiouracil, and diiodotyrosine plus methylthiouracil respectively.

Administration of methylthiouracil alone caused, as might be expected, a considerable increase in the parenchyma content of the thyroid, whereas the absolute amount of colloid substance remained unchanged.

Administration of sodium iodide alone resulted in an abso-

lute increase in the amount of colloid substance. Diiodotyrosine and sodium iodide (when equivalent with regard to iodine) both have the same repressing effect on the cellular hyperplasia caused by the simultaneously added methylthiouracil; but they bring about an absolute increase in the amount of colloid substance despite the concurrently administered methylthiouracil.

These investigations were supported from The King Christian den Tiendes Funds.

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## X-RAY EXAMINATION OF PANCREAS AFTER INSUFFLATION OF AIR INTO STOMACH

By

*Svend Ludvigsen, Assistant Physician.*

X-ray examinations of the head of the pancreas after development of air in the stomach were first carried out and published by Lysholm & Engell in *Acta Radiologica* 15: 635, 1934.

The method used by these writers consists in administration of effervescent powder, whereby carbon dioxide is developed in the stomach. With the patient lying prone a lateral radiograph is taken with horizontally passing rays. The pancreas is then seen as a soft-tissue shadow projecting into the air shadow of the stomach. Lysholm & Engell have examined a number of patients in this manner and obtained very fine results. The method does not seem, however, to have been applied in practice by subsequent investigators; at least no such examinations have been published since.

In my experience it is difficult to keep the necessary amount of carbon dioxide in the stomach from the patient has taken in the effervescent powder till he is placed in the prone position. The patient will often discharge the air by mouth.

I have modified the method by inserting a duodenal tube through the nose. The position of this tube should be controlled by visualisation, so as to make sure that the end of the tube has reached the stomach. The patient is then placed in the prone position on a low wooden box, after which air can be insufflated through the tube. The insufflation may be carried out in different ways. At first I used oxygen blown in from an oxygen-holder by means of a rubber bag, but later on I changed to ordinary atmospheric air insufflated through a Janel's syringe. The amount of air applied cannot be indicated, but

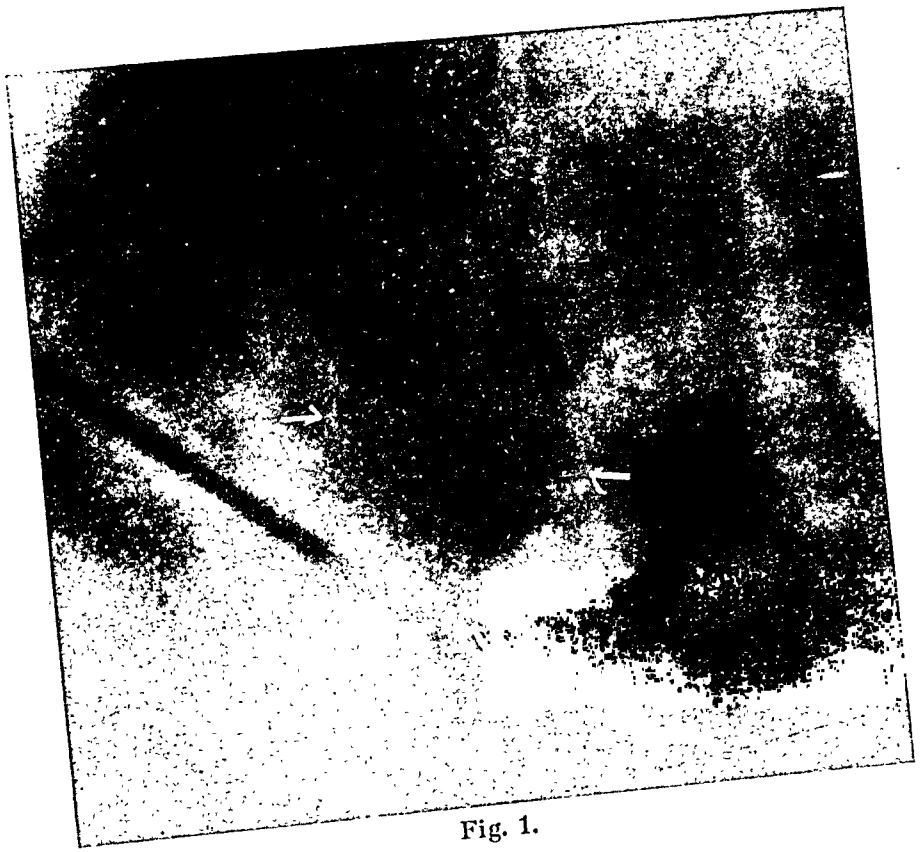


Fig. 1.

the insufflation is stopped when the patient gets a feeling of tension.

Lysholm & Engell state that the normal pancreas corresponds in size to the breadth of 1 vertebral body. The truth is, however, that the normal range of variation of size is rather great. The contrasting power of the pancreas may likewise vary considerably, because this gland often presents fatty degeneration. It is, therefore recommended to take several pictures with X-rays of different degrees of hardness, and to repeat the examination several times.

The demonstrable pancreas enlargements may have different causes. The enlargement due to a massive tumour localized in the pancreatic head is the easiest to diagnose, because such a tumour is most plainly visible on X-ray films. Flat pancreas tumours are more difficult to ascertain, even when they extend



Fig. 2.

into the retroperitoneal tissue. (However, the above method should make it possible to diagnose any enlargement of the pancreatic head).

By using this method in the X-ray Department, Bispebjerg Hospital, we succeeded in radiological demonstration of pancreas enlargement due to insuloma in one case, pancreatitis in another (Fig. 1), and cancer in a third (Fig. 2).

Case 1. A. Q. Man, aged 50. Dept. D.

Transferred in April 1943 from the psychiatric department. Had for 10 years had convulsive attacks of ab. 10 minutes' duration with spasms of arms and legs. No biting of the tongue, and no discharge of faeces. In addition he had had minor fits of absence of a few minutes' duration. The condition had become aggravated within the past 6 months; the attacks had increased in frequency, while at the same time he had been feeling tired and lost weight. Came to the hospital in an ambulance car, having fallen ill in

the street. On admission he was comatose with snoring respiration. His extremities were cool and cyanotic. Positive Babinski's reflex in the right leg, doubtful in the left. Blood pressure 120/180. Pulse rate 92. Temperature 36.9° C. Blood sugar 10 mg. per cent.

Recovered consciousness immediately after intravenous injection of glucose.

Insuloma being suspected a special examination was made of the pancreas, which was seen to be enlarged, projecting ball-shaped into the air-filled cavity of the stomach. On operation the tail of the pancreas was found to be transformed into an irregular, hard tumour, which was removed.

Histological examination showed the tumour to be an adenoma of the islands of Langerhans.

The case is not illustrated, because the X-ray films were lost after having been lent out.

#### Case 2. A. M. A. Man, aged 59. Dept. B.

Admitted in December 1946 with a sense of pressure in the epigastrium and under the right curvature of 14 day's duration. Tiredness and headache. Normal temperature. Shortly before admission there occurred jaundice. Icteric index 160, bile pigments + + +, benzidine + +, diastase 150. Abdomen obese. A somewhat enlarged liver seemed palpable. X-ray of abdomen: nothing abnormal. Colon (after instillation of contrast medium): nothing abnormal. X-ray of the pancreas in January 1947 revealed, at the site of the pancreas, a large tumour projecting into the air-filled cavity of the stomach. The jaundice subsided during stay in hospital, and the patient was discharged on Febr. 13, 1947 feeling perfectly fit. A follow-up examination of the pancreas on April 28, 1947 showed that the enlarged pancreas shadow had diminished. X-ray diagnosis: pancreatitis.

#### Case 3. L. S. F. Man, aged 65. Dept. B.

Cholecystostomy in 1910 because of cholelithiasis. Since 1922 intermittent colitis cases. Repeatedly admitted to Dept. B for colitis. Readmitted in November 1946 with pain in the left side of the abdomen of 9 month's duration. No palpable tumour on admission.

X-ray of colon, kidneys and urinary ducts, pelvis, and column: nothing abnormal except for prostatic hypertrophy. X-ray of stomach and duodenum revealed duodenal ulcer. Benzidine +. In February 1947 a resistance was felt under the left curvature. X-ray examination after insufflation of air into the stomach revealed a large, smooth, soft-tissue shadow at the site of the pancreas. Diastase 150. On operation there was found a tumour adherent to the left kidney and the spleen with ingrowth through the mesent-

ery to the colon. The patient died 4 days after the operation. Necropsy finding: cancer of pancreatic tail with penetration into kidney and mesentery. Metastases to liver and spleen.

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 Weekly Clinical Pathological Exercise, *ibid.*, 235, 521-523, 1946.

sota, back in the early twenties, namely, that the operative mortality in cases of exophthalmic goiter coming from the portion of the United States west of a line drawn north and south through the state of Indiana (roughly 650 miles west of New York City and 2000 miles east of San Francisco), was significantly much greater than in otherwise similar cases coming from east of the above mentioned line. Plummer had this to say about these findings: "Irrespective of other possible differences, I am convinced that the number of cases that will attain a status in which death is imminent, and hence in which it is easily precipitated, is not the same throughout the world. Evidence suggests that the incidence, as well as the number of patients who reach a crisis status, is different in adjacent counties throughout the northwestern states."

Plummer did not attempt to carry his interpretation further, nor can I, but the point I would like to make is that he has presented evidence that a geographical factor (nature unknown) plays a role in the determination of a thyrotoxic patient's ability to withstand the shock of thyroidectomy.

During the last war I attempted to learn something of the geographic factors of thyroid disease by corresponding with all the medical alumni of the Massachusetts General Hospital in the armed forces. These men, as medical officers, were scattered over nearly the whole globe. I asked them what they had observed both among military personnel and in civilian populations of countries in which they were assigned to duty. Almost invariably the reply was that they saw no Graves' disease or thyrotoxicosis in personnel of the armed forces whatever, either in men or women, in active theatres of operation or in base areas. Of civil populations they hadn't enough experience to be able to give any significant information. Seemingly if psychic trauma can precipitate thyrotoxicosis, it is either a different type of psychic trauma than that encountered in warfare, or the type of individual who succeeds in passing military induction boards is not one susceptible to the development of this abnormality.

One correspondent told me of a dozen or so cases of typical Basedow which had occurred in a large camp for German prisoners of war in North Africa.

Among the civil population at home during this period we saw plenty of patients with Basedow, and almost invariably they gave a history that the symptoms had followed shortly after a husband or son had gone overseas, or the news had arrived that he had been killed, wounded, or was missing in action.

Thus it appeared that the disease, even in wartime, is one of civilians, not of the military. I do not know the significance of this fact either, but nonetheless I found it an impressive one.

When the war was over in the summer of 1945, I learned first through a letter from Dr. Kurt Iversen, who wrote to me on the suggestion of Professor Meulengracht and of Professor Eggert Møller, of the remarkable epidemic of thyrotoxicosis which occurred during the occupation of Denmark by the Germans. Dr. Iversen furthermore informed me that Norway had experienced a similar increase in the incidence of the disease, but of less magnitude. Subsequently I received also verbal accounts from Drs. H. M. Jersild and Arne Barfred, who visited my clinic in Boston, and finally from Professor Meulengracht himself, who kindly addressed the Staff of the Massachusetts General Hospital on the subject on October 16, 1947. The prompt subsidence of the epidemic after the liberation of Denmark, of which he informed us and showed his data, was no less remarkable than its inception.

After I had heard of the Danish epidemic I began questioning all of our medical guests from other countries about their experiences in their own lands. From Professor Paul Govaert of Brussels, who visited my clinic in January of 1947, and from the paper of Bastenie, and from other Belgians, I learned that during the occupation of Belgium nothing at all comparable to the events in Denmark was observed. Indeed Basedow's disease appears to have been both milder and less frequent in Belgium during the occupation than in previous times of peace. There was, however, an increase in the incidence of simple goiter. Bastenie suggests that the mildness of hyperthyroidism may have been the result of the ingestion of antithyroid substances in the diet, which of necessity was high in cabbage and such vegetables. The suggestion has also been made that half starved persons simply cannot develop full blown thyrotoxicosis.

From Professor Charvat of Prague I learned that in Czechoslovakia the thyrotoxicosis of Basedow had been mild during the war and many of the cases could be classified as *formes frustes*.

I did not succeed in getting any information suggesting striking changes in Holland, France, or Italy in either incidence or severity of the disease during the war, but I was informed by Professor Antonio G. Sison of Manila that he was certain there had been an increase in the Philippines during their occupation.

What now do these things signify? The most direct approach to this question is, perhaps, to ask wherein did conditions differ in Denmark and Belgium. Both countries were occupied by the enemy. In both, doubtless, there were plenty of psychic traumata, but in Belgium there was in addition food shortage, which was not a factor of significance, I am told, in Denmark. Whether this difference in nutritional states in the two countries explains the difference in incidence and severity of Basedow, or whether other more subtle factors were operative, can only be guessed at.

The theory that the nutritional state is important is militated against by the fact that years ago Plummer observed in the piping times of peace, in well fed Minnesota, an epidemic of toxic goiter bearing some similarity to that in occupied Denmark.

During the years following 1923, and reaching a peak in 1926 and 1927, the incidence of cases of exophthalmic goiter in the region adjacent to Rochester, Minnesota rose to three or four times that of any preceding period. The epidemic had completely subsided by 1931. Nothing similar to this occurred in the eastern parts of the United States, nor so far as I am aware, in any parts but those mentioned by Plummer.

No definite conclusions can be drawn from the scattered and fragmentary facts to which I have referred. However, they do indicate that geographical factors may play some role in the etiology, or pathogenesis, of Basedow's disease, and certainly they offer an invitation to further exploration. It is important, I am sure, that as much accurate data on the incidence and severity of Basedow's disease, and from as many countries as

possible, be gathered for periods both of peace and war, and of scarcity and plenty. This information should be gathered if possible in a cooperative manner, so that data from one region could be easily compared with that from another. It would be, so to speak, an enterprise in geo-endocrinology.

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## PROCTOSCOPY, SOME TECHNICAL AND CLINICAL NOTES

By  
Otto Moltke, M. D.

The following remarks will probably seem very trite to those who are intimately acquainted with proctoscopical examinations. It is my conviction, however, based partly upon conversations with colleagues, partly upon information from patients, that technical details capable of facilitating the procedure, are very often omitted, and that certain minor findings of diagnostic importance are overlooked by a great number of examiners of the lower bowel. Hence these brief remarks.

### *Technical.*

The general principles of proctoscopy are well known and will not be repeated here. Moreover, a rather ample literature will supply the novice with sufficient advice regarding them. (Strauss, Bensaude, Manson-Bahr, Bockus.) Let it suffice here to make the following technical comments.

*Preparation of the patient.* It is generally assumed that no proctoscopical examination can be made without the preparatory cleansing of the patient's bowel. Usually he will be given an enema on the previous evening — now and then after a cathartic — and not rarely this is followed by an opiate to keep the bowel at rest. So far I can judge, this procedure in many cases is superfluous in the least, and to some extent liable to confuse the result of the examination. Superfluous, because in the majority of cases the proctoscopical examination is easy to make on the unprepared rectum, and misleading in cases of colitis and dyschezia. The rectum and the distal part of the sigmoid are empty in normal individuals, the faecal mass not reaching farther than the descending colon, and thus the bowel will easily permit the tube to penetrate up to 25 cm. If, however, the rectum and sigmoid are packed with faecal matter,

or if there is such an amount of discharge of blood and pus that the inspection is seriously hampered, proctoscopy must be repeated after due preparation, having thus demonstrated the actual presence of such pathological conditions as mentioned. If the only purpose of proctoscopy was the demonstration of dysentery, ulcerative colitis, polyposis, cancer or other grave disorders, the preliminary cleansing of the rectum would in a way be justified; but as the scope of the examination also comprises far less serious conditions, but nevertheless very disagreeable to the patient, only demonstrable in the unprepared patient it ought to be postponed till a first sight has proved it necessary. Moreover, in most cases the diseases mentioned above can be seen very easily with no special preparation, so this can be confined to those in which the view is obscured.

The routine procedure in our department is therefore that patients so far are not "prepared" for proctoscopy. We only ask them to empty the bowels (if possible) and the bladder immediately before the examination; and only if this does not suffice, they get an enema on the preceding evening combined with an injection of a spasmolytic just before the examination.

*Introduction of the proctoscope.* A digital exploration should always precede the introduction. Not only can fissures, hemorrhoids and small tumours just inside the anus thus easily be detected, but the examiner can reach a rectal carcinoma or a lymphogranulomatous stricture, and by the mere touch of his finger get very far into the diagnosis. But moreover: by the rectal touch one facilitates the introduction of the proctoscope through the lubrication of the anus and the slight relaxation of the sphincter following the dilatation by the finger.

The proctoscope should never be introduced without being warmed a little. If the tube is cold it may cause spasms, especially in sensitive individuals, and rectal spasms are convenient neither to the patient nor to the proctologist.

I hope it is generally accepted by now that the proctoscope should be introduced under the guidance of the eye, and not blindly. According to *Strömbeck*, this method has been in use at least in Sweden in some places, and has undoubtedly been responsible for some cases of perforation of the rectum.

As a rule, the introduction of the tube, even to its full length,

does not irritate the patient very much. Before the introduction, the patient should be warned that he probably will feel some discomfort but no pain, and it is of great importance that he keeps quiet and that above all he must make no sudden movements during the examination. As a matter of fact, the introduction of a tube 30 cm. long *must* cause a certain discomfort, but this is the same kind of feeling — a sense of distension — as the “call to defaecation”. Actual pain occurs in cases of spasms in the rectum or sigmoid, when the tube is driven too forcibly against or through these, and occasionally in women, when the proctoscope enters and passes the sigmoid flexure. This is rather common in the premenstrual period and probably due to some ovarian disturbance (hyperaemia?) connected with it. However, one thing *does* trouble the patient, and having tried it once they are often greatly afraid of a new examination. This one thing is the insufflation of air, so often, so indiscriminately and so unnecessarily practised. If the patient is placed in the knee-elbow position — this being the most convenient for the purpose, the abdominal contents sliding upwards and thus making the rectum free from kinks and pressure from the upper abdominal organs — insufflation of air should be limited to very few cases. Generally speaking, it is possible — provided that the examiner takes the trouble to follow the anatomical course of the bowel — to introduce the tube up to 20 cm. without insufflation. After this point it may be necessary to insufflate a little air to widen the rather narrow space in the sigmoid, but it should be done with great care and only by the examiner himself and under the guidance of his eye. In old people with a loose and sluggish mucosa, insufflation may be of advantage in the rectum itself. It must be emphasised that you may blow any amount of air into the bowel without any result of value to the examination, if the tube is placed anatomically wrong, and if it is placed rightly, you will generally have no reason to enlarge the space. In some cases the examiner will be delayed by spasms in the rectum and sigmoid. Attempts to force these or to widen them by insufflation will, as a rule, only make them more obstinate. Sometimes they will relax after a little patient waiting, but in more severe cases it may be helpful to give an injection of a spasm-

lytic (for instance Trasentin), after which they will rapidly disappear. Especially in such cases it is very disagreeable to have the bowel blown full of air; the feeling of distension is very acute and the pain may be very distressing.

These remarks refer to the knee-elbow position. If other positions are used, such as the dorso-lateral (Sim's position) or the lithotomy position, some insufflation will be unavoidable, the whole rectal tube being more compressed in these. Excepting the cases where the patients for some reason or other cannot endure the knee-elbow position (e.g. weak and elderly persons) this ought to be the position of choice. The sense of indecency which some attach to it (why, by the way, is this position more indecent than the lithotomy position?) can generally be relieved by the tactful conduct of the examiner, who never should allow proctoscopy to be a "show", and always perform the examination with the help of a single assistant in cases of nervous and anxious patients.

*Removal of the tube.* When removing the tube the examiner should re-examine the walls of the bowel very closely. Special attention should be given to the last centimetres of the rectum, this part very often being not examined at all, which is a pity, as it often is the site of minor catarrhal inflammations (anitis, cryptitis).

As a general rule it should be emphasised that the proctoscope should be guided by a firm but gentle hand. Rough movements, and any use of force, must be avoided, remembering that "only fools dash in, where angels fear to tread". It is essential that the patient is quiet and beforehand knows what is going to happen, and that the examiner keeps in constant touch with him regarding any feeling of pain and able to predict if a possibly painful step is taken.

### *Clinical.*

The clinical findings may be divided into 1) commonplace changes with no pathological significance, 2) pathological changes of a certain but not vital consequence, and 3), those of real importance to the patient's health and life.

1) A very trite, often overlooked, and now and then misinterpreted condition found in the rectum is *melanosis recti*.

This term is used of a certain pigmentation of the mucosa, dark-brownish in colour, in advanced cases with a vivid yellow reticulation network between the dark patches ("load's back"), described in this country by *Erik Madsen*. Melanosis is probably caused by deposits of pigments derived from laxatives of the anthracene group; at least, it is most commonly found among addicts to these. It is often overlooked, which does no harm, as it seems to be of no pathological importance; sometimes it is taken for a certain sort of proctitis, which is worse. If only it is known, it should not be mistaken.

2) A very common cause of rectal complaints is rectal constipation. The patient may or may not have regular daily movements, and if he has, he has a very marked feeling of not being sufficiently evacuated. This causes great discomfort, making him feel distended and "full", and it is generally accompanied by flatulent dyspepsia, itching at the anus, and hemorrhoids. Left alone this condition may result in a "ball-valve accumulation" of the rectum. Digital exploration in such cases will already reveal a faecal compaction in the rectum, but by this means of course it can only be traced 10 cm. above the anus. Upon introduction of the proctoscope one will find the whole rectal canal filled with more or less hard faeces completely obturating the bowel. It is extremely difficult to find one's way through this faecal column, and a second examination must be performed after cleansing of the bowel. If the cleansing is done beforehand as a matter of routine, one is liable to miss the diagnosis, which is of real importance to the patient's future well-being after proper treatment.

In cases of "colitis" — this very misleading term being used here of the colonic states following constipation and misuse of laxatives, characterized by stercoral diarrhoeas alternating with constipation, distension of the abdomen, flatulence etc. — a very characteristic picture is often seen at proctoscopy in unprepared patients. The rectal wall in such cases is seen to be completely coated with liquid or semi-liquid faeces, covering the mucosa, which has to be wiped clean with cotton-wood to obtain a view. Care should of course be taken to make sure that it really is only a colitis, and that no malignant lesion hovers behind.

Other minor disorders, which are often overlooked, are the

catarrhs of the anus. If the tube is removed too quickly, one is almost sure to miss the last few centimetres of the rectum and the anal channel. Apart from fissures and hemorrhoids, which are unlikely to escape attention, the rectal outlet is often the seat of superficial catarrhal conditions (anal cryptitis, simple anitis). These catarrhs are better inspected through the anoscope, but a properly performed proctoscopy should reveal them to the examiner. In such cases the anus will present itself with a dark red surface with the characteristic stellate striped pattern in cases of cryptitis. Such disorders often causes pain, itching and other discomforts in the anal region.

3) The graver disorders comprise cases of inflammation, dysentery, simple haemorrhagic proctitis, ulcerative colproctitis, polyposis, and strictures of an inflammatory and malignant nature.

Dysentery in the Scandinavian countries is mostly of bacillary origin and will not present any features of special interest. Amoebic dysentery in our regions is sporadic (sailors and other persons having been in the tropics); attention in these is directed towards the small abscesses in the wall of the ampulla.

Haemorrhagic and ulcerative procto-sigmoiditis is characterized by an oedematous, deeply red, readily bleeding mucosa, partly covered with mucus and pus. The condition is diffuse in the parts involved. Circumscribed bleeding should always awake the most lively suspicion of cancer. Actual ulcers are only rarely met with. One may safely admit that the more untrained the examiner is, the more ulcers will he think he sees, small sub-mucous haemorrhages often being mistaken for ulcers. It is only in very severe cases of ulcerative colitis that ulcers may be found, and as a rule these patients are unable to undergo proctoscopy; or if they are, the tube will readily be filled with such an amount of discharge that inspection is made impossible. The ulcers may, however, be felt by digital exploration ("raw beef") —.

Regarding the polyposes I would refer to the remarks concerning cancer.

Inflammatory strictures are rarely met with. Now and then a case of ulcerative colitis heals with the formation of a stricture. These are funnel-shaped with dense walls, impossible to pass. Well known is the stricture found in lymphogranuloma venereum (Syndrome of *Jersild*). In fully developed cases these

strictures can hardly be mistaken: localized 6—8 cm. inside the anus, causing a diaphragma-like, very hard gristly wall, impossible to force either with finger or with the proctoscope, completely different from the strictures found in cancer.

The greatest and by far the most serious problem for the proctologist is the possibility of a cancer in the areas covered by the proctoscope. In the rectum itself there should be no difficulty, in so far as the tumour ordinarily is felt very easily with the finger, and visualization only serves to ascertain the size and type of the tumour. If situated in or in the immediate neighbourhood of the sigmoid flexure, the tumour will present itself either as a polypous tumour projecting into the lumen of the bowel or as an ulcerous crater in an otherwise completely normal mucosa. In early cases the tumor may be so small that the tube is likely to pass over it, and it may be overlooked if the examiner is not on his guard. But in the more proximal parts of the bowel, it will very often be impossible to visualize the carcinoma. Attention is here directed to two points. First: isolated polyps in this region should always awake suspicion. Taken as a whole, polyps very often disintegrate into malignancy and should *per se* be considered a possibility of later carcinomas. But moreover, Buie has shown that a carcinoma in the sigmoid often is accompanied by small polyps at a distance from the tumour ("sentinel polyps"). If therefore a polyp is seen in the sigmoid, the examiner should make the greatest effort to penetrate further in search of a carcinoma, which may be found a few cm. proximal to the polyp. Secondly: another sign is what might be called "rectal spittle": in an apparently normal bowel the passage is suddenly barred by a rather violent spasm, and through this is passed an amount of muddy-grey or bloody mucus, which may fill the tube. This sign, which is almost pathognomonic for cancer, by no means indicates that the tumour is situated immediately above the "spittle". It may be located 10—15 cm. above it. But nevertheless: having seen this sign, you may safely turn the patient over to the surgeon.

Proctoscopy should not be the property of highly specialized surgeons. It ought to be a method of examination which every practitioner was able to undertake, and every gastroenterologist performed as a matter of routine. The minor diseases of the

rectum and sigmoid are often very distressing to the patients and not difficult to treat and cure if they are known and detected in due time. And the prognosis of rectal and sigmoid cancer is mostly dependant upon the early diagnosis of the lesion. Too much health is wasted and too many lives are lost because of too little attention to this rather simple examination.

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## ON THE MECHANISM OF GLYCOSURIA. II<sup>1</sup>)

Factors affecting the Appearance and Duration of Glycosuria.

By

A. Levin Nielsen, M.D.

It was already in 1917 that *Hamman & Hirschman* (6) were able to show how glycosuria begins at a higher blood sugar level than that at which it disappears. This observation has been confirmed many times since and has become known particularly through the work of *Faber & K. M. Hansen* in 1923 (3). *Hallehol* (7) agreed, but showed that the "threshold", defined as the blood sugar value at which glycosuria occurs or recedes, is sometimes the same on ascending and descending blood sugar curves, indeed that occasionally it may be higher on the descending curve.

In addition to these observations, *Faber & K. M. Hansen* (3), *Hallehol* (7), and *Sakaguchi et al.* (14) demonstrated that it was nothing uncommon for glycosuria to occur up to half an hour after the blood sugar curve had passed its peak.

Hitherto there has been but little comprehension of the exact mechanism of these finds, complicated as it is by the fact that it is possible on rare occasions to show on a descending curve that glycosuria comes again shortly after it has subsided.

In the discussion on the causes of these curious phenomena of glucose excretion the opinion was soon formed that purely mechanical phenomena cannot be the deciding factor. For the threshold on ascending curves the reason seems to be mostly that the sometimes considerable time interval between the peak of the blood sugar curve and the onset of glycosuria is difficult to reconcile with our knowledge that the passage from

<sup>1</sup>) These studies were carried out with the aid of the Christian X Foundation.

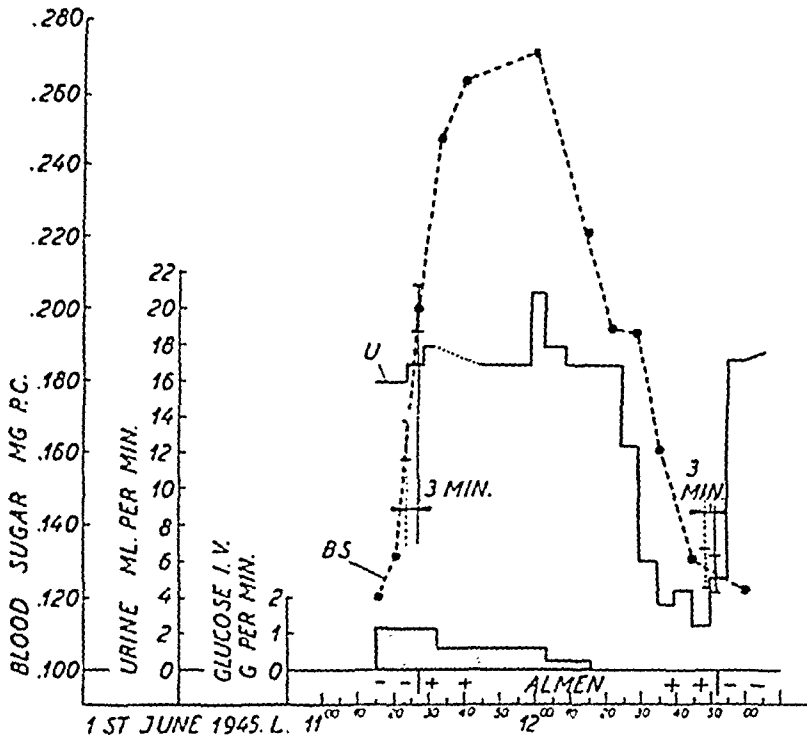


Fig. 1. Blood sugar, glycosuria and diuresis during threshold determination and lessening urine output.

blood to bladder takes only a few minutes when tested with various substances such as iodide (Roux (13)), salicylate (Hallehol (7)), phenol red (Smith 1938 (18)), methylene blue, inulin and diodrast (own investigations).

Regarding the cessation of the glycosuria, *Faber & Hansen* (3) and *Hallehol* (7) point out that the delay is much too great merely to represent the time taken by the passage from kidneys to bladder, so that other factors must presumably play some role. These unknown factors are acknowledged somewhat hesitatingly by *Shannon & Troast* (17), who speak of "hysteresis", whereas *Peters & van Slyke* (11) "find no evidence in the experiments of *Shannon & Fisher* that the relation of reabsorption to filtration follows one principle while the blood sugar is rising and another when it is falling". As we know, *Shannon & Fisher* (16) in dogs found a constant upper limit for glucose reabsorption, a phenomenon which *Smith et al.* (4)

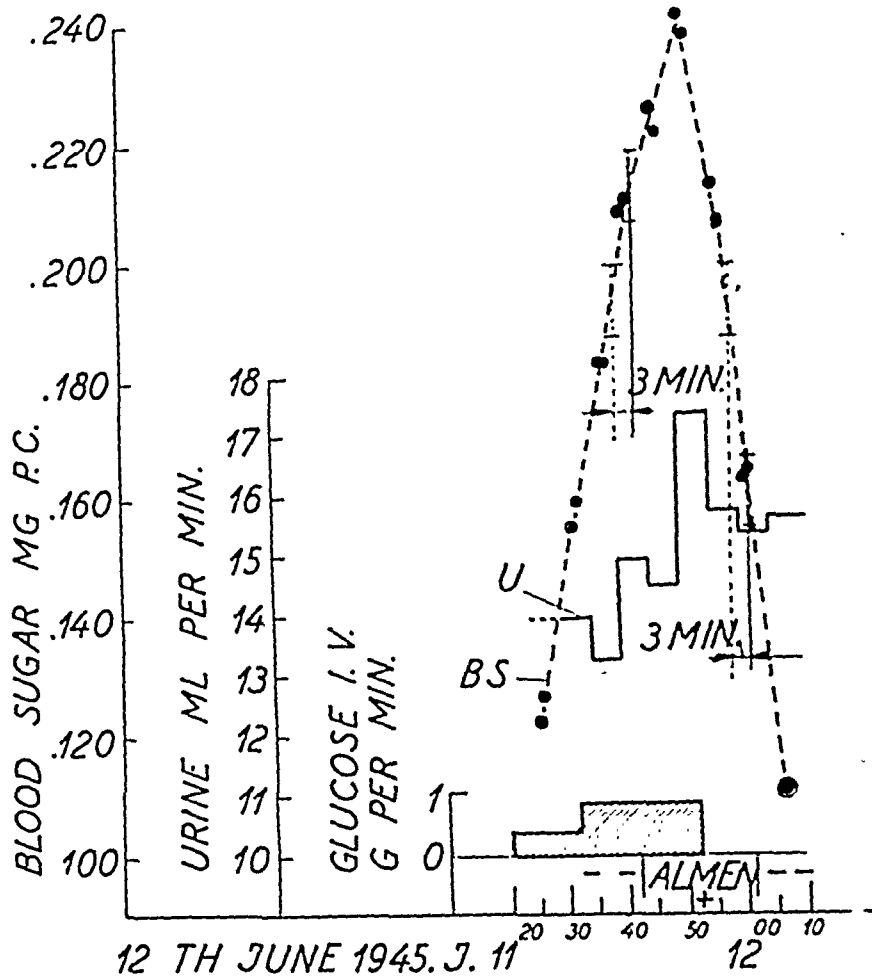


Fig. 2. Threshold determination during constant urine output.

and the present author (10) have shown applies to man as well.

### Own Experiments.

For the purpose of investigating to what extent the purely mechanical flow of the urine through the kidneys and urinary tract can influence the coming and going of glycosuria, I have made various series of experiments: a) determinations of the "threshold" on ascending and descending blood sugar curves under continuous intravenous infusion of glucose, partly at falling or low diureses, partly at uniformly high diureses; b) observation of the occurrence and cessation of glycosuria

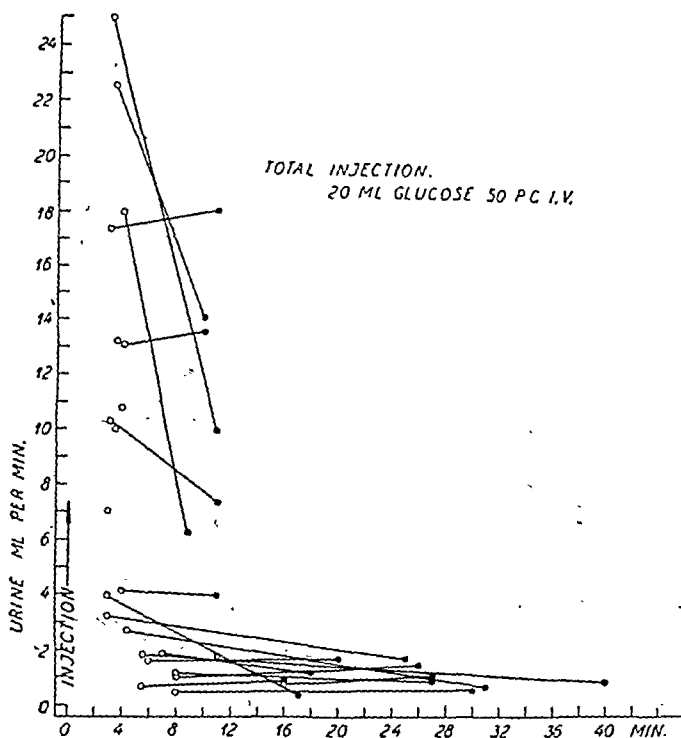


Fig. 3. Relation of diuresis and appearance and duration of glycosuria after 20 ml 50 % glucose, injected i.v.

after the rapid injection of a single dose of glucose as previously described by Robinson et al. (12); c) quantitative determination of the glycosuria from minute to minute after single injection; d) certain orientative investigations of the output of simultaneously injected glucose, inulin and diodrast.

*Methods.* All the experimental subjects were normal with healthy kidneys, lying with the catheter á demeure throughout the test. The urine was collected in periods of from 30 seconds to 2 minutes. The blood sugar was determined according to Hagedorn-Norman Jensen's method, the urine output first qualitatively by Almen's test, later quantitatively as well by Krarup's modification of Hagedorn-Norman Jensen's blood sugar method (9). The inulin was determined by the diphenylamine method (1), the diodrast according to Bak, Brun & Raaschou's modification of White & Rolf's method (2).

*Results.* As an example of experiments with continuous glu-

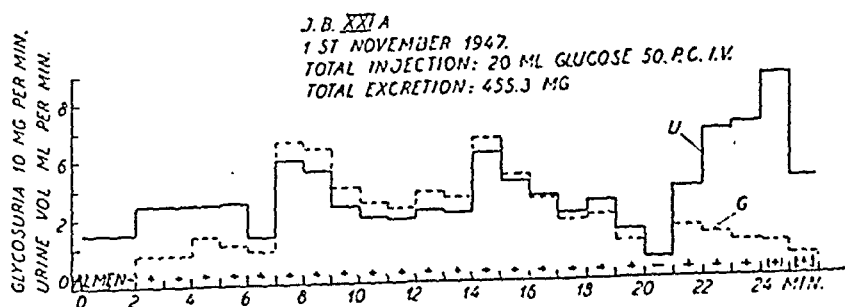


Fig. 4. Quantitative determinations of glycosuria during low diuresis.

cose infusion I give two graphs, one (fig. 1) compiled from an experiment with falling diuresis in conjunction with the cessation of the glucose infusion, the next (fig. 2) from another subject with a high, steady diuresis. In both experiments the threshold on ascending curves is higher than on falling curves, but the curves show that a displacement of the thresholds to a point three minutes earlier (the dotted line) will not make the thresholds the same in the first experiment, but that it will do so in the second. Similar tests on five different individuals, first with low or falling, then with high, steady diureses, every time gave similar results: at low and especially at falling diureses there is a great difference in the thresholds on ascending and descending curves, and a shift of  $2\frac{1}{2}$  to 3 minutes does not abolish the difference, whereas it does so at higher, steady diureses. The principal reason for this is that on descending curves the threshold moves upwards, but on ascending curves it is lowered only slightly or not at all. Whereas the boundary between negative and positive Almen reactions is very sharp at both low and high diureses, the boundary from positive to negative is somewhat blurred, especially at the high diureses.

In the next series the purpose was to ascertain when glycosuria sets in after the injection of 20 ml. 50 % glucose intravenously in the course of 15 to 30 seconds. A total of 23 tests were made on 20 healthy subjects. The results are shown by fig. 3. In the graph, glycosuria commencing between  $2\frac{1}{2}$  and 3 minutes is shown as commencing 3 minutes after the injection, and so on. In 17 tests the duration of the glycosuria was also determined. At high diureses it lasts only a few minutes, but

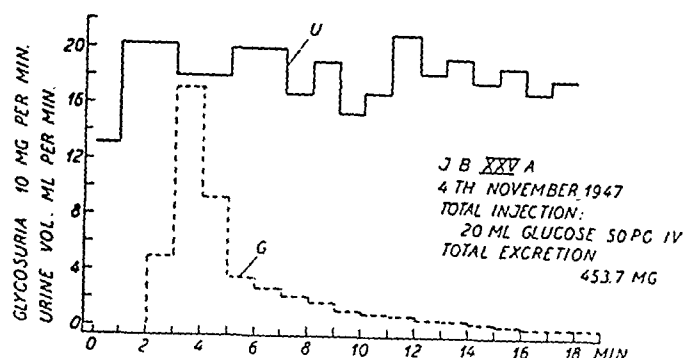


Fig. 5. Quantitative determinations of glycosuria during high diuresis in the same individual as Fig. 4.

with minute diureses of under about 2 ml. the glycosuria sets in later and lasts much longer, up to as much as 40 minutes after the moment of injection.

The third series comprises twelve curves of the glucose output after intravenous glucose injection as in the foregoing series. The glycosuria was determined from minute to minute by Krarup's urine-sugar method (9). As examples I give two graphs from tests on the same subject. In the first test the diureses were low, in the second high. It happens that the total glucose output in the two tests was practically the same, but the curves look very different (figs. 4 and 5). In some of the tests the glycosuria terminated after a steady fall, to reappear for a few minutes after a pause of one or two minutes. At the same time the Almen reaction became positive again.

Finally, one of six curves from the simultaneous injection of glucose and diodrast (fig. 6). The other five curves with diodrast and inulin do not, at the high diureses employed, seem to present features that are much different, although one shows that the excretion of diodrast may commence before glycosuria. I have not yet gone into the question of the explanation of this latter result.

Finally, in tabular form I have set up the results from some comparative tests of the value of the glycosuria in the same subject. The tests were made by collecting all the urine at a low diuresis in one portion from the moment of injection until

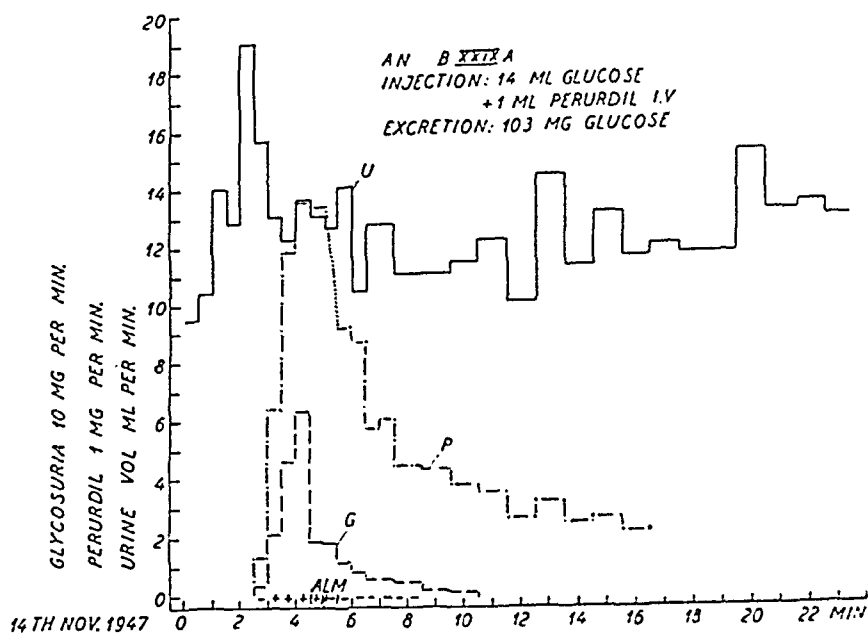


Fig. 6. Quantitative determinations of glucose and diodrast ("Perurdil") in urine after rapid intravenous injection.

45 minutes later, then, after water drinking and commencing higher diuresis, again 45 minutes after a new glucose injection.

Table 1.

Glycosuria after 10 g. glucose intravenously in 4 subjects at various diureses.

Test	Diuresis ml./min.	Total glycosuria (mg.)
I a	2.18	90.5
I b	2.87	92.9
II a	0.8	89.1
II b	9.7	126.8
III a	0.54	59.6
III b	4.6	77.3
IV a	0.44	59.9
IV b	4.8	47.2

### Discussion.

a. The "threshold". The threshold referred to in this article is now out of date. According to results now available, the blood sugar value is reduced to a factor which, together with the value of the ultrafiltrate, decides how much glucose is ultra-

filtered. The ultrafiltered quantity of glucose is reabsorbed to a certain upper limit, beyond which glycosuria sets in. Therefore, glycosuria occurs as the result of the interplay of opposing forces, and the blood-sugar value at which glycosuria appears, being a passive physiological value, is only of secondary interest. Nevertheless, it was through determinations of this "threshold" that the various peculiarities in the excretion of glucose were first observed.

b. *Delay time.* In the first series of tests it was shown how a displacement of about three minutes at high, steady diureses is capable of removing the difference between the thresholds on ascending and descending blood sugar curves, but not at low or falling diureses. The reason for shifting the curves about three minutes is clear from the graph of the single injections, fig. 3: in all tests with diureses of over 4 ml. the glycosuria appears almost just as long after the commencement of the injection, whereas at low diureses it appears somewhat later. However, the diuresis plays a much more important role in the cessation of the glycosuria than in its onset. Although the tests in fig. 3 were made on different subjects, who therefore must have had very different glucose outputs, the glycosuria was quickly over when the diuresis was high, whereas it sometimes continued for as long as 40 minutes after the injection when the diuresis was low.

c. *Determination of "threshold".* From the graphs for the quantitative output, followed minute by minute in the same subject in two tests with different diureses (figs. 4 and 5), it will be seen that though the excreted quantity of glucose is the same, at high diureses it lasts for 16 minutes, with the greater part within the first 8 minutes, whereas at low diureses the duration is 24 minutes with the greater part within 18 minutes. As the glucose output in the two tests, in which the conditions otherwise were uniform, were the same, it is reasonable to assume that the kidneys functioned equally in the two tests up to the moment when the urine had passed the place of reabsorption in the tubules, and that it is a purely irrigation phenomenon when the glycosuria continues so long at the low diuresis. In other words, the problem of the difference in the

threshold on ascending and descending blood-sugar curves is reduced to one of suitable technique for the determinations, which can only be done properly with high diureses. As the time of the passage of the glucose from blood to bladder cannot be forced down under two or three minutes, even when the diuresis is very high, it will always be necessary to compensate for this by employing as the genuine threshold values the blood-sugar values  $2\frac{1}{2}$  or 3 minutes before glycosuria sets in or disappears.

The quantitative investigations have also shown that slight traces of glucose can be recovered long after the Almen reaction has become negative. As these faint traces may be regarded as the result of the irrigation phenomenon — they will also be present after tests with glucose infusion through the catheter in the bladder — it will be an advantage when determining the threshold to employ the less sensitive Almen reaction and reckon exclusively with definitely positive reactions.

d. *How does the excretion of glucose differ from that of other substances?* The purpose of testing the excretion of diodrast ("Perurdil") and inulin injected together with the glucose was merely to show how, after a single injection, the glycosuria quantitatively corresponds very closely at first to the excretion of a non-threshold substance. The two excretion curves do not divide until the initial increase is passed, as the excretion of the threshold substance quickly ceases, whereas that of the non-threshold substance continues along a steadily falling curve. At low diureses the only difference of importance in this connection is that the glycosuria continues so much the longer owing to the low diuresis. It is this connection between diuresis value and glycosuria duration that has not been clear to earlier workers and has appeared so conspicuously in threshold determinations on falling blood-sugar curves. By virtue of the threshold value on ascending curves there has been a fairly accurate idea of when the glycosuria properly "ought" to have subsided, and its long continuation at low diureses has been assumed to be something that must be specific for glucose. After what has been shown above this is not so. The advantage of glucose is merely that, because it is a threshold

substance, we can form an idea of how long its passage through the kidneys takes, in contrast to non-threshold substances which are excreted as long as they occur in the blood.

Even in the early literature it is possible to find hints at the slow excretion when diuresis is low; as long ago as in 1917 *Sansum & Woodyatt* (15) reported that in experiments on a dog with continuous infusion of glucose, in conjunction with falling diuresis there was a heavy fall in the glucose output, this being compensated for by a corresponding extra-excretion in the subsequent clearance period. As regards urea, *Joliffe, Shannon & Smith* (8) in 1932 showed how the dead space, as they call it, may utterly ruin clearance determinations. This does not seem to have been noticed much in recent literature.

#### *Summary.*

The author shows how, with intravenous glucose loads and high, steady diureses, the blood-sugar values are the same about three minutes before the onset of glycosuria and its cessation. He also shows that the value of the diuresis determines the appearance of the glycosuria and even more so its subsidence after single injections of glucose intravenously. The lengthy passage when the diuresis is low is scarcely specific for glucose, but must be assumed to apply to all substances. Clearance determinations on falling diureses are therefore fallacious.

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## SEX HORMONE ANALYSES II<sup>1)</sup>

The Excretion of Sexual Hormones by Normal Males, Impotent Males, Polyarthritics, and Prostatics.

By

K. Pedersen-Bjergaard, Ph. D. and M. Tønnesen, Phar. D.

Undoubtedly the best way of ascertaining the production of hormones by the human organism is by continuously following the concentration of these substances in the blood. With regard to the gonadotrophic, androgenic and oestrogenic hormones, however, their content in the blood is so low that it cannot be determined with certainty for the normal organism. Accordingly, we are constrained to test the excretion in the urine, for with the full 24-hour diuresis it is possible to make an extract with a hormonal concentration so high that the biological titres can be secured. At the same time the method has the advantage that it gives an expression of the total output of the organism throughout the twentyfour hours, whereas blood analyses show merely the concentration of hormones at the time of taking the sample.

### *Technique.*

A brief summary of the technique used is given below. As for further details see *Pedersen-Bjergaard & Tønnesen (1948)*.

*Gonadotrophins.* The gonadotrophic hormone is precipitated from the full 24-hour diuresis as follows: Add 7 ml. acetate-acetic acid buffer, pH 4.75, per litre urine, and then 20 ml. of a 10 % tannic acid solution per litre urine. Centrifuge, and make a solution of the precipitate with 45 ml. of borate buffer at pH 9.5 as described by *Thomsen & Pedersen-Bjergaard (1936)*, after first washing it in several portions of absolute alcohol and acetone. The resulting solution can now be titrated on infantile female rats for its content of

<sup>1)</sup> *Sex Hormone Analyses I. Oestrogenic, Androgenic and Gonadotropic Substances in the Urine of Normal Women.* K. Pedersen-Bjergaard and M. Tønnesen: *Acta endocrinol* I, 38, 1948.

gonadotrophin. By 1 R.U. is understood the quantity of gonadotrophin required to produce a trebling of the uterus weight of rats 26 days old. The accuracy of the gonadotrophin determination is about  $\pm 30\%$  when three animals per dose are used.

*Androgens and oestrogens.* The androgenic and oestrogenic substances, which are present in the urine partly in the free state and partly combined with glycuronic acid, are extracted, after adding 40 ml. concentrated sulphuric acid to hydrolyse the combined compounds, with 500 ml. carbon tetrachloride per litre urine. The mixture is heated for two hours in a reflex-condenser flask in a waterbath. The heat applied should be sufficient to make the  $\text{CCl}_4$  boil briskly. The  $\text{CCl}_4$  fraction is drawn off separately, 500 ml.  $\text{CCl}_4$  per 1000 ml. urine are again added and boiled again for two hours. From the total  $\text{CCl}_4$  extract all  $\text{CCl}_4$  is distilled off in vacuum. The extract thus obtained, containing the total quantity of both androgenic and oestrogenic substances from the 24-hour urine, can now, after solution in vegetable oil (olive oil), be titrated biologically: on castrated cocks for the androgen content and on ovariectomized female mice for the oestrogen content.

a) Oestrogens: By 1 M.U. is understood the quantity of hormone required to produce complete vaginal cornification in half the number of adult, ovariectomized female mice (*Kemp & Pedersen-Bjergaard* (1933)). The accuracy is about  $\pm 25\%$  using six animals per dose, and about  $\pm 40\%$  using 3 animals per dose.

b) Androgens: 1 C.U. means the quantity of hormone injected intramuscularly required to produce a growth of 20 % in a capon comb. The value in this paper was determined according to *Jensen, Pedersen-Bjergaard & Tonnesen* (1944), a method in which the biological test is made on capons by application to the comb. 1 C.U. is reckoned as  $400 \times$  the quantity of hormone which, administered on the comb in the course of four days, on the fifth shows an average increase of 20 % of the comb area, which very closely agrees with the quantity of hormone which, injected intramuscularly twice daily in the course of four days, on the fifth shows a corresponding increase of the comb area. The accuracy of the biological determination is about  $\pm 50\%$  when five animals per dose are used.

### *Material.*

The investigation comprises the measured excretion of about 2000 male persons, on which were made 2836 quantitative deter-

minations of androgenic substances. In addition, quantitative determinations of gonadotrophic substances were made on about a third of the material.

*The material is divisible into six sections:* The first section, which comprises the excretion of gonadotrophic and androgenic substances in the normal male organism from the age of 2 to 87 years, represents the values of a total of 2389 hormone analyses carried out in the course of nine years (1937—1945).

The second section, comprising the excretion of gonadotrophic, androgenic and oestrogenic substances in the normal male organism, represents the values of 371 hormone analyses made in a single year (1943).

The third section, covering the daily excretion of androgenic substances, and in some cases of gonadotrophic and oestrogenic substances, of five normal males of the ages between 14 and 31 years, the tests being made over periods of from 30 to 120 days.

The fourth section, comprising the excretion of androgenic and gonadotrophic substances of impotent males aged from 20 to 75 years and representing values from 379 hormone analyses.

The fifth section, comprising the excretion of androgenic and gonadotrophic substances of males suffering from Polyarthritidis chronica in the ages from 26 to 71 years and representing values from 17 hormone analyses.

The sixth section, comprising the excretion of androgenic and gonadotrophic substances of males with Prostata hypertrophy in the ages of 31 to 85 years and representing values from 51 hormone analyses.

### *Results.*

The excretion of androgenic substance by normal boys and men in the ages from 2 to 87 is shown in fig. I. The excretion of male hormone cannot be measured until about the age of eight years. Whereas from 8 to 15 years the excretion increases only slowly to about 3 C.U., there is a rapid increase from the age of 15. At about the 20th year the excretion has reached the maximum, amounting to between 10 and 12 C.U. per 24 hours, at which level it is maintained until the age of 35. From 35 to 55 there is a slight decrease in the excretion of androgenic

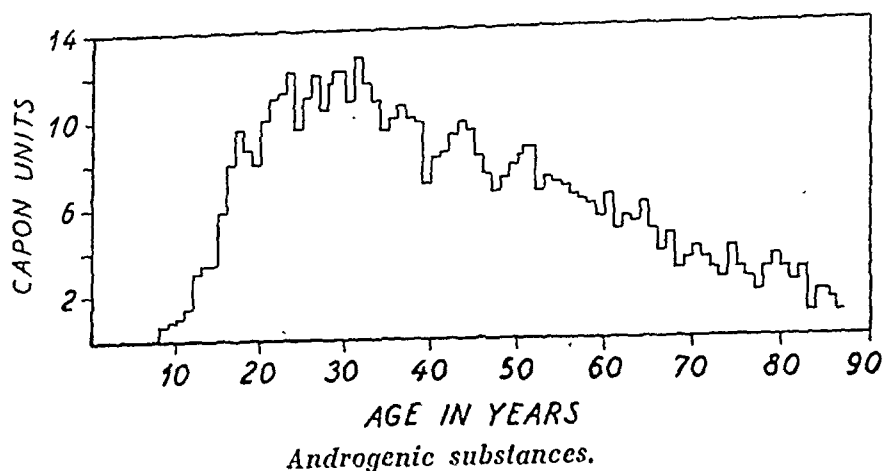


Fig. I.

The average excretion in the urine of normal boys and men expressed in capon-units per 24 hours. The average excretion is between 6.6 and 12.2 C.U. per 24 hours in the ages between 16 and 55 years.

substance from 10 to 7 C.U. in the 24 hours, a decline which continues steadily from the age of 55 with a velocity of about  $\frac{1}{6}$ th C.U. per annum. On the whole these results concur with those published by *Hamburger & Halvorsen* (1942).

By the aid of the photometer *Nathanson, Towne & Aub* (1941) found an extremely small but constant excretion of androgenic substances by boys between the ages of 3 and 8. This excretion increases somewhat between 8 and 11 years, whereupon it rises considerably simultaneously with the development of the secondary sexual characters.

Fig. II shows the excretion of gonadotrophic hormone by normal boys and men of the ages 2 to 87 years.

Measurable quantities of gonadotrophin cannot be found until the age of 8 years is reached, whereafter it rises evenly and as from the 15th year has attained to an average value of 6 R.U. per 24 hours. The excretion remains at this level during the subsequent 40 years, until at about the age of 60 it begins to rise again.

From the age of 60 the average excretion is 15 R.U. in 24 hours.

*Nathanson, Towne & Aub* (1941) found no gonadotrophin in

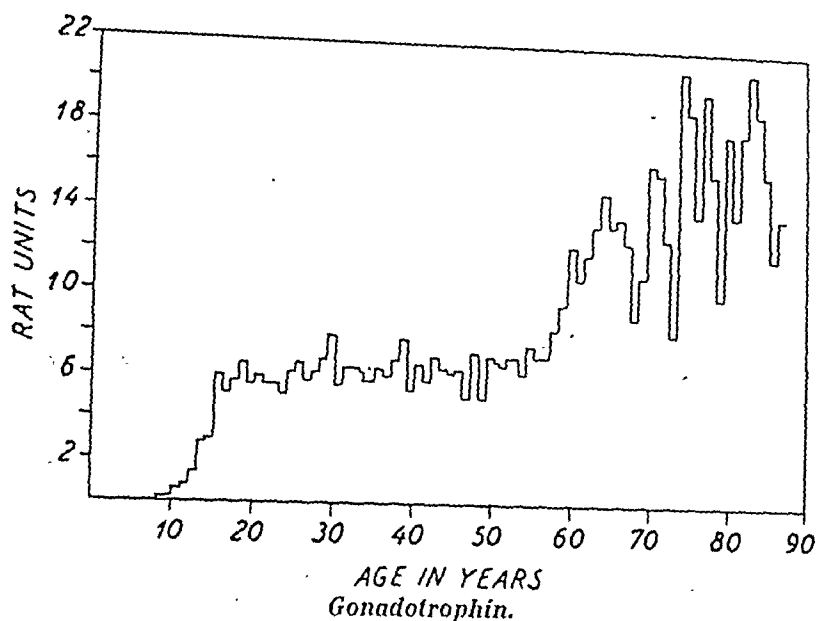


Fig. II.

The average excretion in the urine of normal boys and men, expressed in R.U. per 24 hours. The average excretion is 6 R.U. gonadotrophic hormone between 15 and 57 years.

the urine of boys until between the ages of 12 and 13; they state, however, that this late occurrence may be due to the imperfections of the analytical method employed (alcohol precipitation, infantile mice).

The increased excretion of gonadotrophin by elderly males was first observed by *Oesterreicher* (1933), who presented his report at the 5th Scandinavian Congress of Psychiatrists in Copenhagen in August 1932. In a later publication (1934) he demonstrated that with the technique then employed he was able to observe the increased excretion of gonadotrophin in 20 % of the elderly men. *Kukos* (1934) observed the increase in 6 out of 17 men between the ages of 70 and 84. *Sæthre* (1935) in a material of 72 men aged 20—43 years found no gonadotrophin excretion beyond 50 M.U. per 24 hours. Of 25 men aged 50—63 years, 16 % had an excretion of more than 50 M.U., and of 50 aged 64—86 years 28 % excreted over 50 M.U. in 24 hours. Among most of the individuals tested *Wallis* (1937) observed increased gonadotrophin excretion in prostatics, of whom 16 out of 20 patients aged 51—81 years gave an increased value.

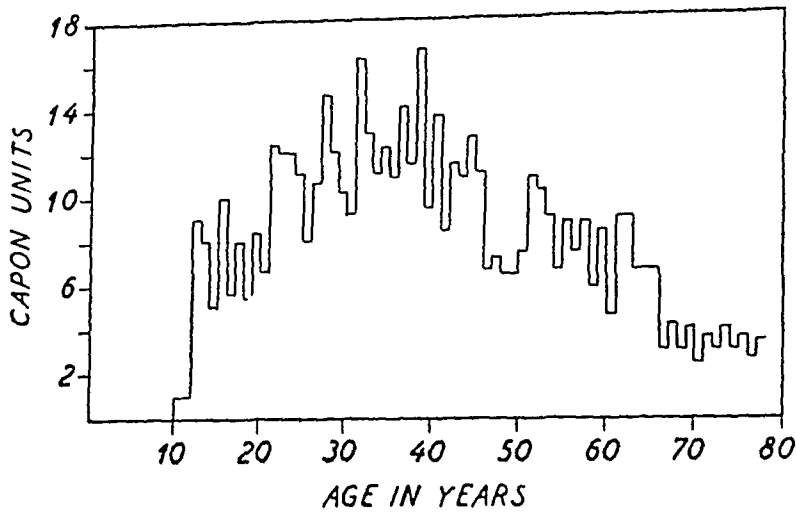


Fig. III.

Average 24-hour excretion of androgenic substances in a single year (1943) from the normal male organism.

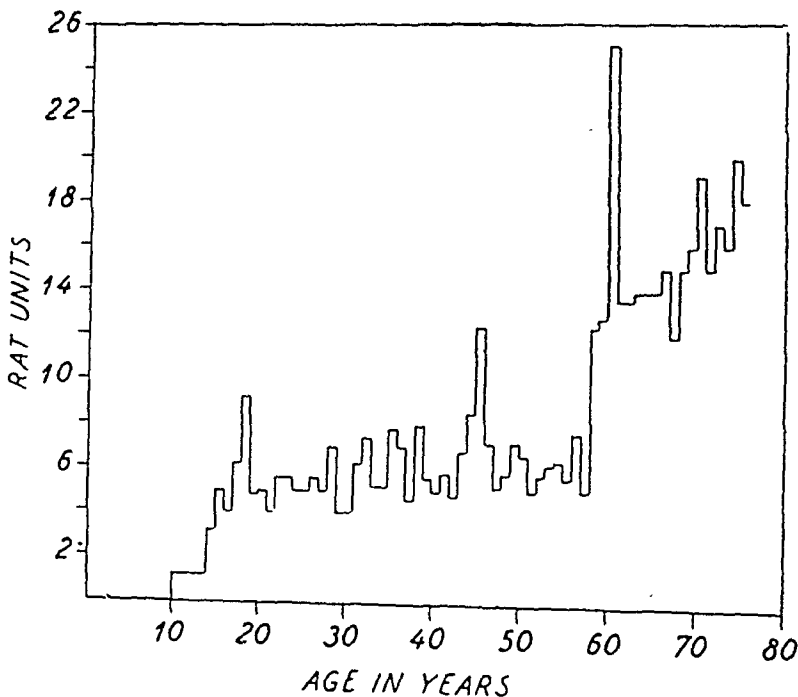


Fig. IV.

Average 24-hour excretion of gonadotrophin in a single year (1943) from the normal male organism.

On the other hand, *Stimpel* (1940) found increased gonadotrophin excretion in only 30 % of prostatics between 69 and 87

years, which agrees well with the aforesaid excretion of normal men of the same age.

To our knowledge, no average curve of the excretion of gonadotrophin by the male organism in a material of any size, such as that shown in fig. II, has ever been published.

The experimental material for a single year (1943), comprising 371 patients, is illustrated graphically in figs. III and IV.

It will be seen from figs. III and IV that the average curves for this one year have a much greater deviation than the corresponding average curves for the nine years of the whole material in figs. I and II. In both instances, however, the trend is the same, viz. falling androgenic substances values and correspondingly rising gonadotrophin values for middle-aged men.

Figs. V to XII show the daily excretion of androgenic substances (in some cases also of gonadotrophin and oestrin) measured during periods from one to four months on five normal males aged 14, 26, 27, 30 and 31 years respectively, and a boy of 12 years.

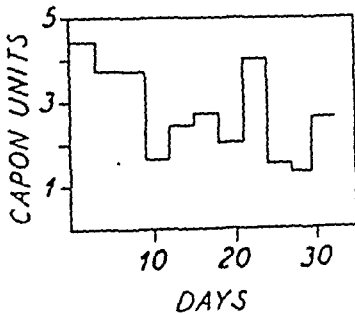


Fig. V.

*C.U. androgenic substances.*

The 24-hour excretion of androgenic substances (C.U./24 hrs) from a boy of 12 years.

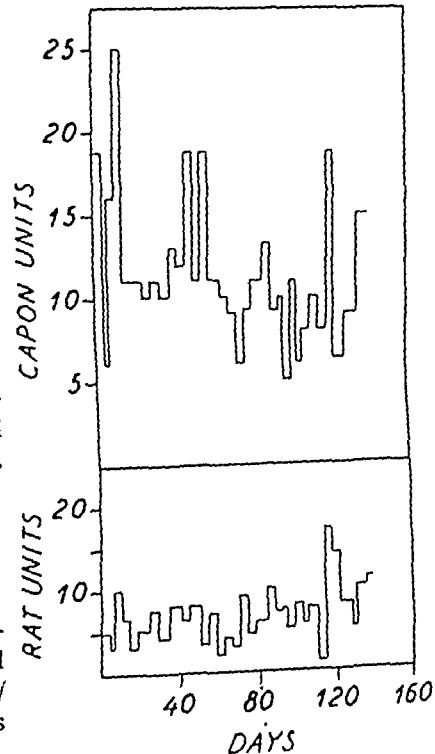


Fig. VI.

*C.U. androgenic substances.*

The 24-hour excretion of androgenic substances (C.U./24 hours) and gonadotrophin (R.U./24 hours) from a youth 14 years old.

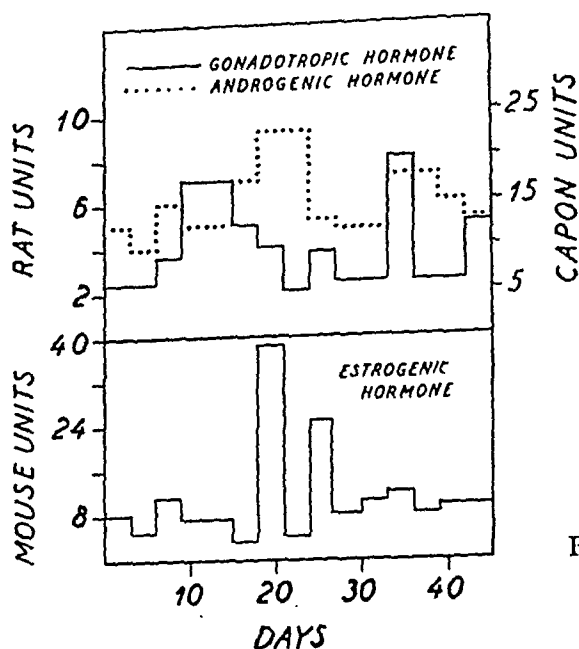


Fig. VII.

The 24-hour excretion of androgenic substances (C.U./24 hrs.), gonadotrophin (R.U./24 hrs.) and oestrin (M.U./24 hrs.) from a 26 year old man.

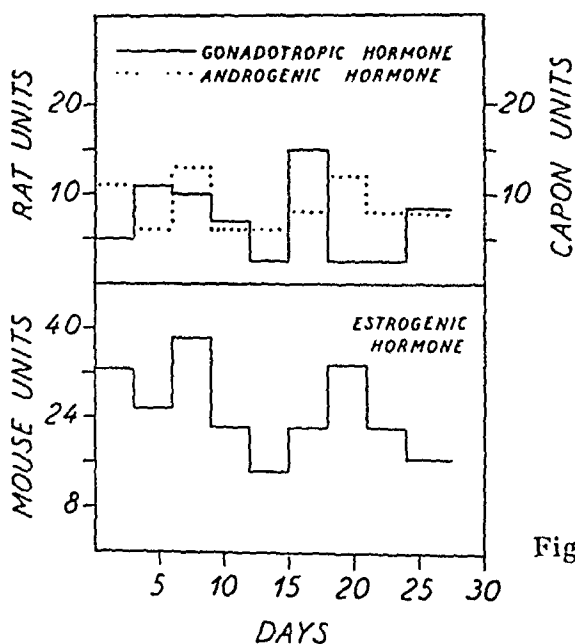


Fig. VIII.

The 24-hour excretion of androgenic substances (C.U./24 hrs.), gonadotrophin (R.U./24 hrs.) and oestrin (M.U./24 hrs.) from a 27 year old man.

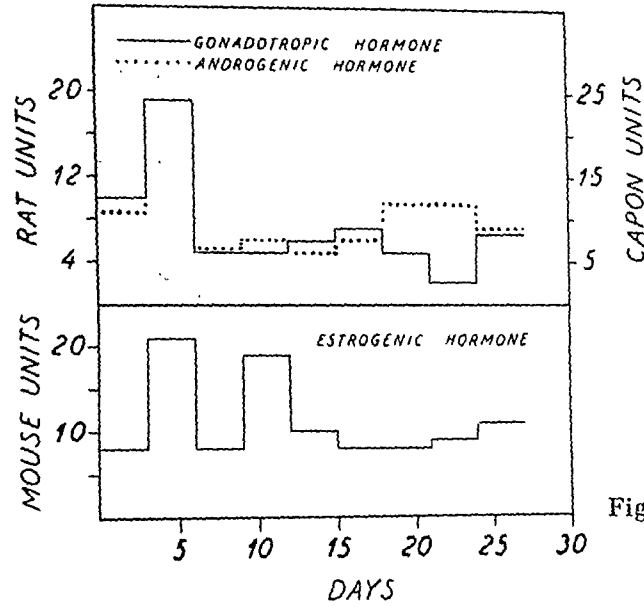


Fig. IX.

The 24-hour excretion of androgenic substances (C.U./24 hrs.), gonadotrophin (R.U./24 hrs.) and oestrin (M.U./24 hrs.) from a 30 year old man.

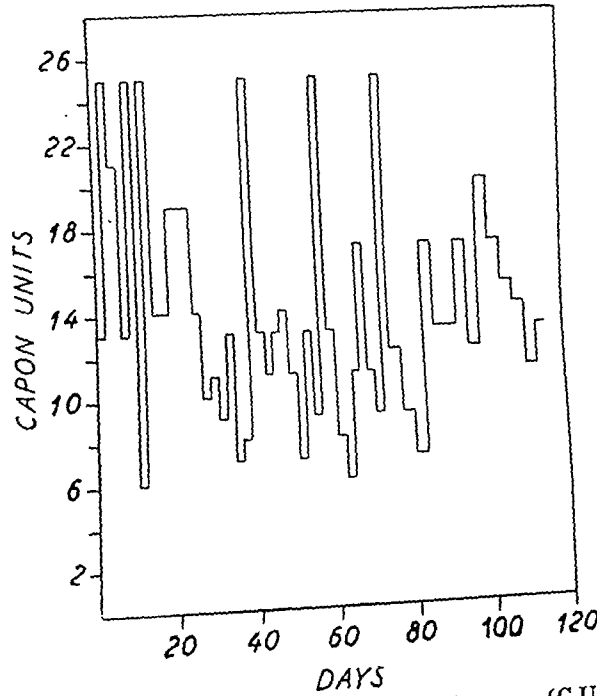


Fig. X.

The 24-hour excretion of androgenic substances (C.U./24 hrs.) from a 31 year old man.

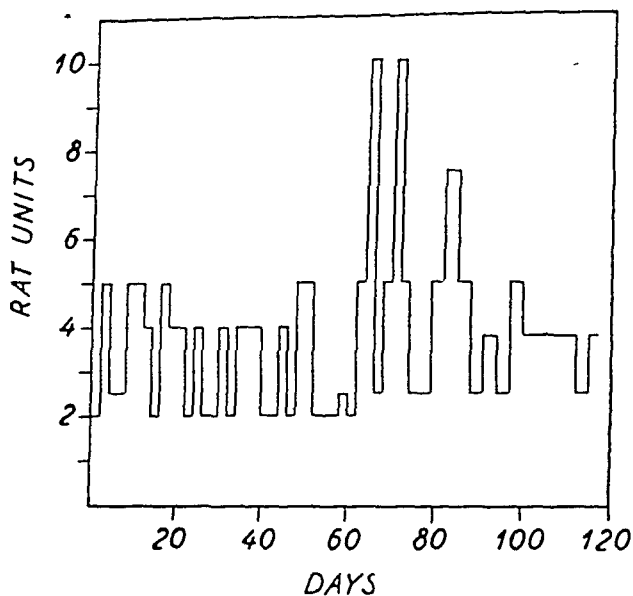


Fig. XI.

The 24-hour excretion of gonadotrophin (R.U./24 hrs.) from a 31 year old man.

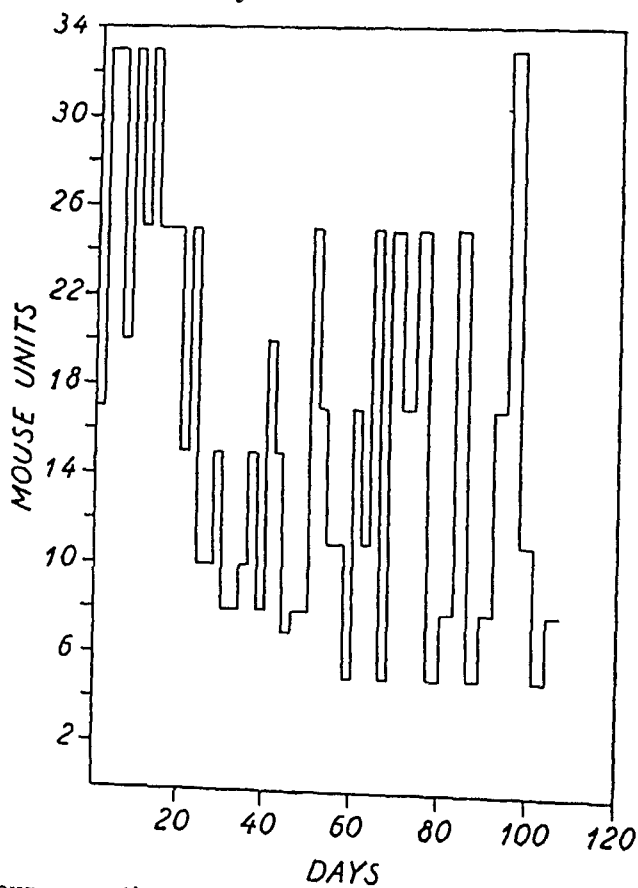


Fig. XII.

The 24-hour excretion of oestrin (M.U./24 hrs.) from a 31 year old man.

It will be seen from figs VI—XII that in this material of normal males the 24-hour excretion of androgenic substances varies from 5 to 25 C.U., and the gonadotrophin excretion from 1 to 20 R.U., whereas there is a variation of from 5 to 40 M.U. in the oestrin excretion. In contrast to what takes place in the female organism, there seem to be no regular fluctuations in the excretion of oestrin, or indeed of the testis hormone, in the male organism; nor, of course, could they be expected.

The greatest variations in the excretion of androgenic substances are expressed in figs. X, XI and XII, in which the analyses during the first 75 days were made on 48-hour diureses, and during the last 40 days on 72-hour diureses. In figs. VII, VIII and IX, in which the analyses are based on four to six-day diuresis, the variations are naturally much smaller, because the high and low values to some extent equalize one another.

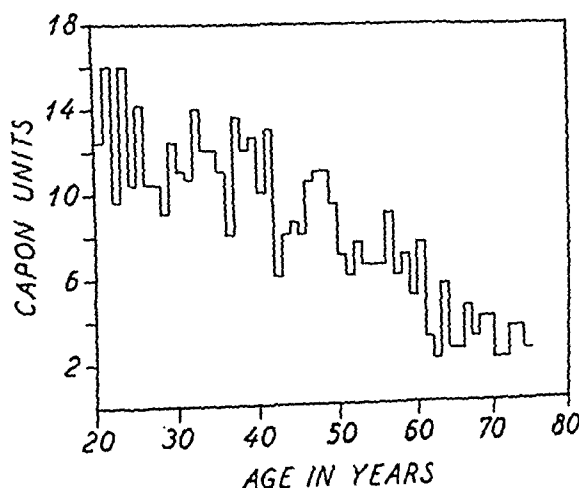


Fig. XIII

Excretion of androgenic substances in the urine of impotent males aged from 20 to 75 years.

Fig. XIII shows that the excretion of testis hormone by impotent men is very much the same as that of normal men of equal age (Fig. I).

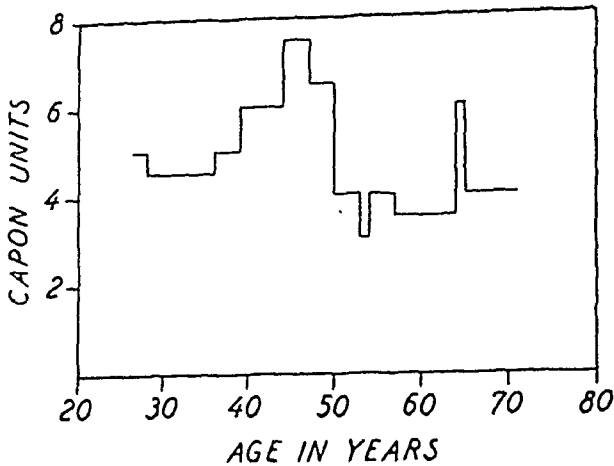


Fig. XIV

Excretion of androgenic substances in the urine of males with Polyarthrititis chronica in the ages from 26 to 71 years.

It will be seen from fig. XIV that for men with Polyarthrititis chronica in the present material the excretion of androgenic substances is practically constant from the 26th to the 71st year. The quantity, which fluctuates round about 5 C.U. per 24 hours, is generally much lower than that of normal males of equal age. It becomes the same only at the age of 65—70 years.

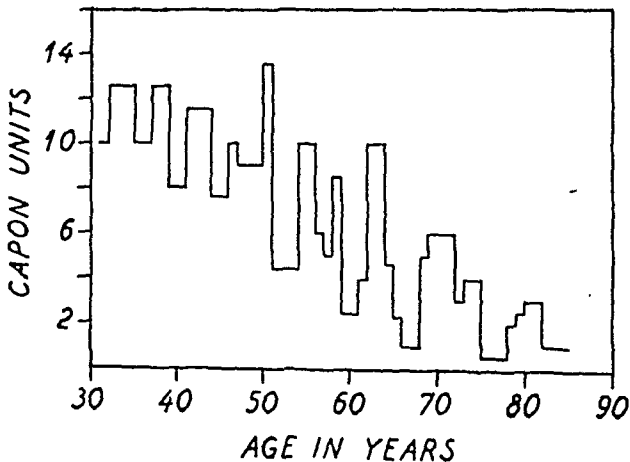


Fig. XV.

Excretion of androgenic substances in the urine of males with prostatic hypertrophy in the ages from 31 to 85 years.

As fig. XV shows, the androgenic substance excretion of males with hypertrophy of the prostate is pretty much the same as that of normal males of the same age (fig. I). This agrees with earlier results communicated by *Borge Heiberg* (1941).

### Summary.

*The normal average excretion.* It is shown by 2389 determinations of androgenic substances in the urine of normal boys and men aged from 2 to 87 years, carried out over a period of nine years, that the excretion does not become measurable until about the age of eight years.

From 8 to 15 years the excretion increases rapidly; at about the age of twenty it has reached the maximum, amounting to between 10 and 12 C.U. in the 24 hours. It remains at this level until the 35th year. From the 35th year there is a slight decrease in the excretion, a decrease which represents about  $\frac{1}{8}$ th C.U. per annum.

Similar determinations of gonadotrophin show that measurable quantities are not excreted until about the 8th year, whereafter the excretion rises steadily until the 15th year, by which time it has reached a value of 6 R.U. in the 24 hours. At this level it is maintained until it begins to rise again at about the age of 60 years. From this age the average excretion is 15 R.U. per 24 hours.

*The normal individual excretion.* Figs. VI to XII show that in the present material the excretion of androgenic substances by normal men varies from 5 to 25 C.U. per 24 hours. The excretion of gonadotrophin varies between 1 and 20 R.U., and of oestrin between 5 and 40 M.U. Contrasting with conditions in the female organism, no regular fluctuations are observable in the excretion of oestrin — or of androgenic substances in the male organism, nor indeed are such regular fluctuations to be expected.

*Excretion by impotent males, polyarthritics and prostatics.* Whereas the average excretion of androgenic substances by impotent men and prostatics was of the same order of size as the average normal excretion, the average curve of patients with Polyarthritis chronica displayed almost a constantly low excretion of the androgenic substances, amounting to 5 C.U. per 24 hours, and it only followed the downward normal curve at the age of 65, where the normal excretion is also 5 C.U.

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## A QUINQUENNIAL SURVEY OF 360 CASES OF ABORTUS PROVOCATUS

By

*Wilhelm Permin and Einar Thomsen*

A wide area within the field of gynaecology, and one that has been growing rapidly during the past few years, is represented by four categories of women who come for consultation:

1. Those who want children but fail to conceive.
2. Those who do not want — more — children but constantly conceive.
3. Pregnant, who repeatedly have premature births or who miscarry.
4. Pregnant, who want their pregnancy interrupted.

It is our experience that the curve for the first category is rising steadily, a rise which in fact was already perceptible during the period of the occupation. The increased interest taken in the clarification of the causal relations in primary and secondary sterility represents some measure of pressure by the population on the gynaecologists who, as a result of modern endometrial biopsy and hormonal analysis, have had their field of activities expanded into regions impossible to survey at the moment, and also have embarked upon the routine testing of the husband's fertility as a natural stage in the solving of the problems.

It is the common experience (1, 2, 3, 4, 5, 6, 7) that the latter category presents a curve with a very steep ascent, especially since 1942. An investigation of the causes would in advance be encumbered with so many sources of error that very large materials alone would have any chance of providing a trustworthy picture of the present situation.

Category 2 is only apparently actual. Its problems are touched upon in the Old Testament; but developments up to advisory sexual clinics and more or less popular textbooks in anticonceptional technique have not so far been followed up with sufficient intensity by professional colleagues. Surgeons have been much too busy with quite other problems, and in Denmark Gynaecologia minor has not yet attained to the position to which it rightly belongs, first and foremost, presumably because major always seems to be greater and more interesting than minor.

For this reason the category has at all times provided good soil for the growth of a more private speciality.

Category 3 is delimitable only in theory. In particular, the domains and boundaries of the so-called spontaneous abortions are vague and concealed, not least because a strict examination of fully reliable anamnestic particulars involves a risk that the physician might have to exchange the confessional chair with the witness-box. Since 1941 there has been an alarmingly great increase in the number of people hospitalized on the diagnosis of Abortus (3), and the etiology of these cases evades a scientific check because their »causa ignota« is a quagmire in which neither the physician nor the criminologist can bottom.

In the following we propose to discuss category 4, fully aware as we are of the weakness of the anamnestic criteria which, according to the laws of Denmark, must be taken into consideration for determining the indication.

In an attempt to draw up a survey of this group of patients and their data we have collected and statistically treated the particulars of all patients admitted for Abortus provocatus to the surgical department of a large Copenhagen hospital during a period of five years, viz. Bispebjerg Hospital's Department F, from the date of its opening. 10th November 1942, till 10th November 1947.

A total of 360 patients were admitted for Abortus provocatus in that period. The operation was performed on 330 of them, whereas 30 were sent away owing to lack of indication; in other words, 8.3 per cent. were refused.

The distribution of the cases over the years was:

	1943	1944	1945	1946	1947	All 1947
Operated .....	22	40	49	102	117	136
Refused .....	3	0	2	10	15	16
Refused % .....	1.3	0	4.0	9.8	12.9	11.7

The last column shows the number of patients for the whole of 1947 in order to illustrate the tremendous increase year by year. The only patient in 1942 is included under 1943.

#### *Age distribution*

Years		Total	Operated	Refused
20 .....	76	21	20	1
20—24 .....		55	49	6
25—29 .....		93	83	10
30—34 .....		90	86	4
35—39 .....	101	73	66	7
40—44 .....		27	26	1
> 44 .....		1	1	0

From this table it is seen — surprisingly enough — that the majority is not made up of quite young women who have »got into trouble«, but of somewhat older people, with a preponderance between 25 and 35 years; moreover, there are many more over 35 than under 25.

The same thing is evident when we take the matrimonial position of the patients:

	Total	Operated	Refused
Married .....	246	222	24
Unmarried .....	66	64	2
Separated .....	26	24	2
Divorced + widowed .....	22	20	2

We find that in by far the greater number of cases the women who wish to have their pregnancy interrupted are married, and not, as many are inclined to think, unmarried or divorced women who want to avoid difficulties in which they have become involved by recklessness. It is decidedly a rare occurrence for moral scruples to drive a patient to her doctor.

It can be of no practical importance to examine which pregnancy of a series is most frequently desired to be stopped. In stead of this we have placed the desire for *Abortus provocatus* in relation to the number of children of the patient already in the home:

Children	Total	Operated	Refused
0 .....	79	76	3
1—5 .....	245	221	24
> 5 .....	36	33	3

Thus it is comparatively rarely childless women who do not want a child, but much more frequently women who already have children at home and to whom another child would mean ruin, physically or economically, all according to their physical or economic resources. How large the flock of children becomes before the various mothers give up thus depends upon each individual's mental equipment and power of resistance. It will be seen that those who do give up do so fairly early, for the mothers with really a lot of children (> 5 children) are represented to a surprisingly small degree.

An examination of environment shows that a third of the patients are working-class people and a third are craftsmen and small traders, whereas the last mixed third includes office people, chauffeurs and cartmen, as well as police people and prison wardresses, about 5 per cent. on each group, domestic servants, teachers, seamstresses, manageresses + supervisors + superintendents, nurses, academicals, each about 2 per cent., and finally artists, students, clinic assistants, farm girls, no occupation, and sundry, each 1 per cent. per group. (The occupations named are of course those of the husband when the patient is married but of no independent occupation).

A survey of the indications supports the impression received from the above that it is more and more because of economic difficulties that the number of women coming in for induced abortion is growing.

	Total	Operated	Refused	1943	1944	1945	1946	1947
Psychiatric ..	108	103	5	5	7	20	40	36
Medical .....	70	70	0	11	17	6	21	16
Eugenic .....	57	51	6	5	8	4	16	24
Social .....	28	16	12	3	4	2	11	8
Mixed .....	92	86	6	1	3	18	23	47
Minors .....	2	2	0	0	0	0	1	1
Rape .....	2	2	0	0	1	1	0	0

This table cannot provide any clear picture; but the marked increase in the mixed indications (in which practically all cases have social indication as one of the components) points strongly to the importance of social considerations; moreover, to those who have spoken to hundreds of these patients it is beyond question that the condition on which the psychiatric indication is based is brought about, or at any rate made worse, by economic worry.

The fact that the eugenic indication is increasing in frequency is probably merely another form of expressing that hereditary research is being carried on with constantly increasing intensity in Denmark.

Finally, it will be seen that the group of »minors« is almost insignificant in size, like the group »rape«. The only two cases in the latter group occurred during the occupation.

The widening activities of the Maternity Aid Institution are clearly discernible:

	1913	1941	1945	1946	1947	Total
+ Institution aid' .....	2	10	14	41	92	159
— Institution aid .....	23	30	37	71	40	201

On examining by whom the patients are hospitalized:

	1913	1941	1945	1946	1947	Total
by hospital department ..	18	29	27	68	45	187
by practising specialist..	7	11	24	44	87	173

we find that more and more are given the indication without being hospitalized while the examination is being made, a state of affairs which must give rise to some misgiving, especially when the basis of the indication is psychic suffering.

In conclusion, a few words about treatment.

During these five years the mortality has been nil, and the complications extremely few. There was no instance of perforated uterus.

Only 36, or barely 11 per cent., had a temperature of over 38° after the operation, and of these the majority had only between 38° and 39° on one evening. And, indeed, chemotherapy was employed only in 7 cases, i. e. in 1.9 per cent.

There were only 5 instances of dangerous haemorrhage, which means about  $1\frac{1}{2}$  per cent. of all operated on; the cause was not that the pregnancy was interrupted too late, as three of the five were in the 2nd-3rd month, but in every case an unexplained, unnecessarily forcible and rapid dilatation of the cervix, which of course should always be avoided. In recent years Department F has always used dilators scaled to open at half numbers instead of whole, and ample time is taken for dilatation. If the cervix is particularly rigid, stipes laminariae is used. Finally, it is now a fixed rule in Department F that the operation is made solely by its regular, trained surgeons, which ensures at one time the most lenient and yet adequate treatment in the shortest possible time.

Stipes laminariae were employed in 82 cases, or 25 per cent. of the operations, a quotient that will certainly fall in the future, because operation in two stages is now employed only when the collum is resistant and there is a fear of tearing by dilatation. When dilatation proceeds smoothly it is possible without risk in all early pregnancies to empty the uterus at once by careful methods and by using uterus-contracting drugs as soon as there is the slightest doubt as to where there is contact with the uterine wall.

Vaginal caesarian section was performed in only one case.

The duration of the period in hospital appears from the following table:

	All patients	Operated	Refused
in hospital $\leq 7$ days .....	147	119	28
"    8—14 " .....	199	197	2
"    >14 days .....	24	24	0

In terms of days this means for

330 operated patients 3098 days  
 30 refused " 119 "  
 Total 3217 days

The average hospital days for all patients = 9 days  
 for operated patients = 9.3 "  
 for refused patients = 3.9 "

At the present cost of about Kr. 30 per day the total cost has

been Kr. 97,000, or about Kr. 270 for each patient admitted for Abortus provocatus.

It is evident from the above survey, and indeed from the experience of others, that the social conditions of recent years form a fertile soil for the future development of the social indication. We therefore feel justified in the opinion that the social problem which Abortus provocatus represents at the moment has been tackled the wrong way about, and that more work along the social lines will presumably reduce hospital activities of this sort. On the other hand, it is pretty certain that the cost of handling the matter in the latter way will be much greater than it is under present conditions.

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## OBSERVATIONS ON BLOOD-REGENERATION IN MAN. VI.

### *Hæmoglobin Regeneration in Patients with Cancer of the Stomach and Intestine.*

By

*E. Schiødt, M. D.*

Anaemia is very common in patients with cancer of the stomach and intestine. Morphologically, this anaemia is not characteristic; hypochromic anaemia is most common but hyperchromic forms are by no means rare.

The number and percentage of anaemic patients and the degree of anaemia is shown in table I, giving the findings of six different investigators. As will be seen, anaemia is found in about 70—80 percent of the patients and the average haemoglobin percentage is about 50—60.

Some authors have tried to go deeper into the cause of the anaemic state by subdividing these patients into different groups. Thus, Mogensen and later Buch, have shown that sex, age, gastric achylia and duration of symptoms have no influence on the degree of anaemia. Mogensen finds no difference in patients with no (or only slight) bleeding and with constant bleeding (gross haemorrhage excepted) and so do Ehrström and Tötterman. Buch, on the other hand, has seen a correlation between haemorrhage and degree of anaemia (table II) Ehrström and Tötterman have found that the relation between the number of patients with cancer outside the pyloric region and the total number of patients with cancer of the stomach is 1:18 in pts. with no anaemia, 6:17 in pts. with slight anaemia and 8:18 in pts. with gross anaemia. They conclude from this that cancer of the pyloric region may act as an irritament to blood-formation. On the contrary, they think that sometimes pyloric cancer may have a destructive influence upon the same function.

Anaemia in cancer, by most authors, has been attributed to

*Table 1*  
*Anaemia in Patients With Cancer of the Stomach.*

Author	Year Criteria of Anaemia	Total Number of Patients	Number of Pt's with Anaemia	Percentage of pt.s with anaemia	Average Hb%	Remarks
Eisen .....	1928	76			52	
Cheney .....	1934 < 4 Mill. r. b. c.	43	31	72	53	Gross haemorrhage
Mogensen .....	1936 M < 90 % hb. F < 80 % hb.	75	52	69	72.8	not included
Elmström & Tötterman	1942 not stated	72	54	75		
Buch .....	1943 < 80 % hb.	418	332	79		
Foged .....	1946 not stated	312	183	59	59	Surgical Department

*Table II.*  
*Anaemia in Relation to Haemorrhage.*  
Buch 1943.

	No bleeding or more than three negative Benzidine reac- tions.	Periodical or slight but con- stant bleeding.	Severe and con- stant bleeding.
Percentage of patients with anaemia	64	81	88
Average haemoglobin percentage . .	70	62	56

haemorrhage, intoxication, malnutrition or loss of auxiliary blood-forming function of the stomach. While Cheney does not find much effect by treatment of this form of anaemia with iron or liver (except secondary anaemia liver fraction), other authors (Mogensen, Gram) have found a rather remarkable power of regeneration in some patients. On the whole, however, the rate of regeneration has not been much investigated.

#### *Own Investigations. Degree of Anaemia.*

The aim of this investigation has been purely practical.

1) Is it in cancer possible from the degree of anaemia or the rate of regeneration to prognosticate e. g. as to the chance of operability or length of survival?

2) Is it possible from the rate of regeneration to aid the differential diagnosis between cancer and ulcer of the stomach?

In all, I have examined 137 pts with cancer of the stomach and 18 pts with colonic cancer. The rate of operability, as compared to the figures of two other Danish investigators, is shown in table III. As in other Danish publications, only a very small — too small — number of patients have been operable.

As many of the patients have been under observation for some time, I can present a maximum and a minimum haemoglobin percentage. The patients have been divided into groups: operability and mortality. As shown in table IV, the minimal average values are quite in accordance with those given in table I.

Still, there is no perceptible differences between those patients who on laparotomy presented a cancer which could be resected, and those who were inoperable. The patients who

Table III.  
*Operability of Patients With Cancer of the Stomach.*

Author	Year	Total Number of patients	Not operated Number	Percentage	Explorative laparotomy (inoperable cancer) Num- ber	Percent- age	Gastro-entero- stomy Num- ber	Percent- age	Resection Num- ber	Percent- age	Remarks
Buch	1943	583	511	88	18	3	31	5	23	4	Med. Dept.
Foged	1946	394	158	40	66	17	88	22	82	21	Surg. Dept.
Schjød	1947	137	104	76	18	13	3	2	12	9	Med. Dept.

Table IV.  
*Anaemia in Own Cancer Patients.*

	Maximal average hemoglo- bin value	Variation	Minimal average hemoglo- bin value	Variation
Patients with cancer of stomach				
Resection .....	82	112—48	57	93—41
Explorative laparotomy ..	82	121—60	53	60—21
Dead .....	70	90—35	46	73—26
Patients with cancer of colon .....	77	110—31	55	88—19

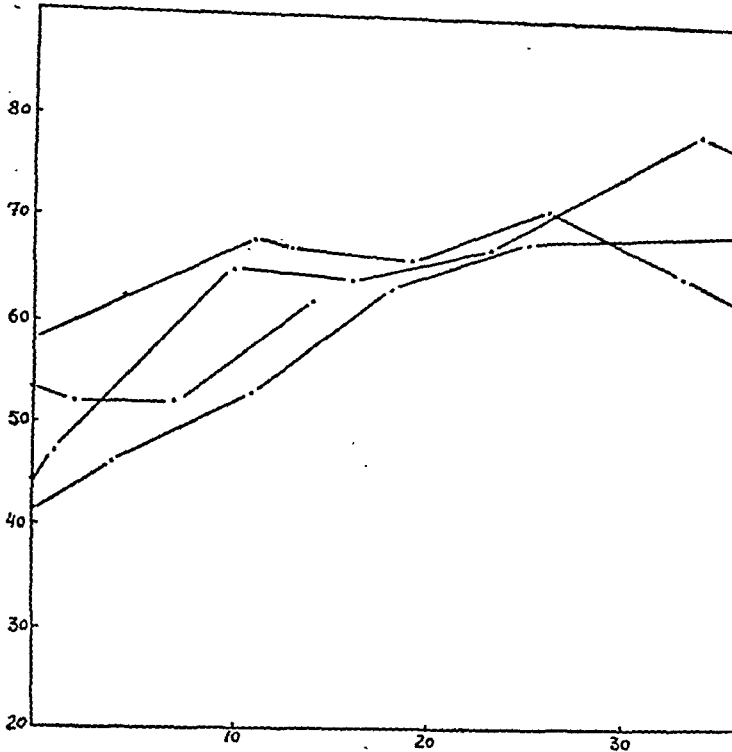
died had a more pronounced anaemia but never to such a degree that any reliable prognosis could be based upon this factor. Some patients died without any anaemia.

There have been too few patients with cardiac cancer (in all 5) to state anything about the difference in degree of anaemia between this site and the pyloric site of the cancer. Anaemia in colonic cancer is very similar to that of gastric cancer.

#### *Regeneration Rate.*

In figs 1—3 haemoglobin regeneration in the groups operable (fig. 1), inoperable (fig. 2) and dead (fig. 3) is shown. It appears that some patients regenerate their blood quite well and that others lag considerably behind, or even show a constant fall in haemoglobin. Even if the operable patients are those whose blood regenerates best, nothing can be said from the regeneration curve as to whether the patients can stand an operation. There are not so many curves because most patients will undergo the operation as soon as the diagnosis is clear after one or two determinations of the blood-level. Anaemia is no contraindication to operation. Some of our patients who had a low haemoglobin percentage (min. 48 percent) had a resection of the stomach with good result. If necessary, the blood-level may be raised by one or more transfusions (fig. 4 shows an example).

The curves in figs 1—3, however, shows spontaneous regeneration or regeneration supported by iron and liver. It appears, then, that patients with cancer of the stomach may regenerate their blood quite well, and better than could be expected from the opinion expressed in the literature on the subject.



*Fig. 1.*

4 patients with cancer of the stomach who underwent resection. The curves date from the period in the medical department before operation. Ordinate: Hb. percentage (100 % hb. = 18.5 vol. %  $O_2$ ). Abscissa: Time in days.

Still, regeneration is so different that no standard for regeneration in cancer can be determined, as I have been able to do in pts with haematemesis or melaena from peptic ulcer or with pernicious anaemia. (12) Therefore, it can not be said whether iron or liver therapy has any effect although this is my impresison.

Some patients with cancer of the stomach have regenerated their blood as well as patients with a peptic ulcer. But in most cancer patients regeneration lags considerably behind this standard.

In fig. 5, I have shown composite curves of haemoglobin regeneration in 16 pts with haematemesis or melaena from peptic ulcer.

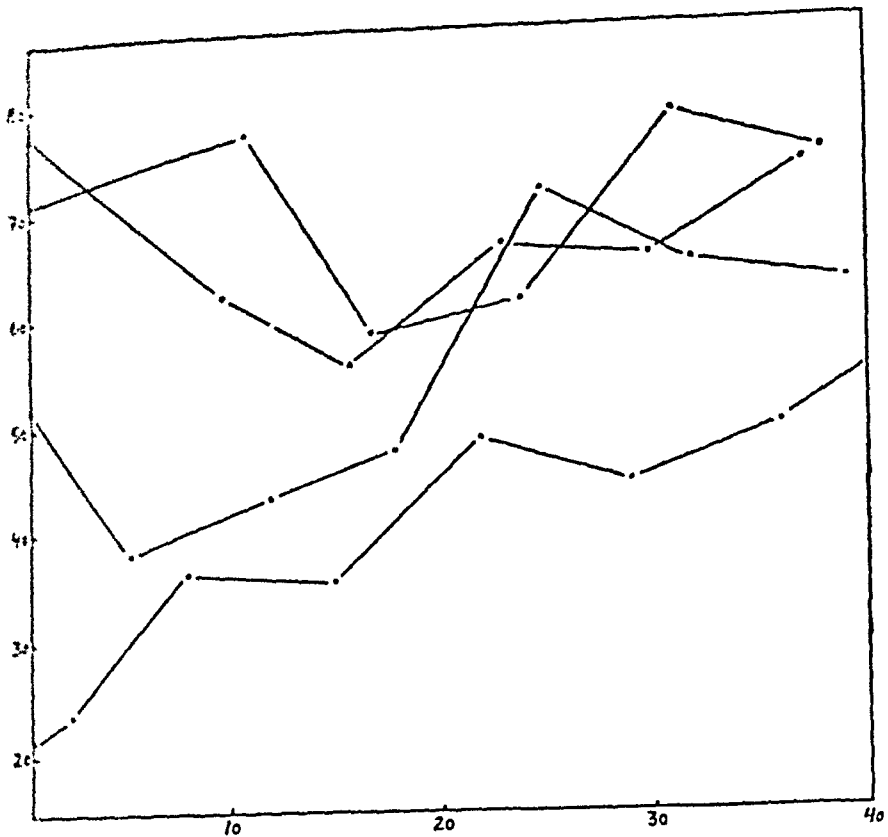


Fig. 2.

4 patients who had an inoperable cancer of the stomach. The curves date from the period in the medical department before operation. Ordinate and abscissa as in fig. 1.

It has long been recognised that constant bleeding, even if slight, is almost pathognomonic for cancer (Thayssen, Holten, Meulengracht & Jensen, Jersild). The lagging regeneration curve, with or without bleeding, has the same importance. If the regeneration is very inferior to that in peptic ulcer, cancer must be highly suspected. (Complications, (of which phlebitis is the most common) may cause a retardation of regeneration in ulcer). In some cases, where the history was indefinite and where X-ray examination failed, a lagging regeneration curve and bleeding, was the only indication for an explorative laparotomy where an operable cancer was found. This has especially been the case in cancer of the duodenum or colon but also in cancer of the stomach.

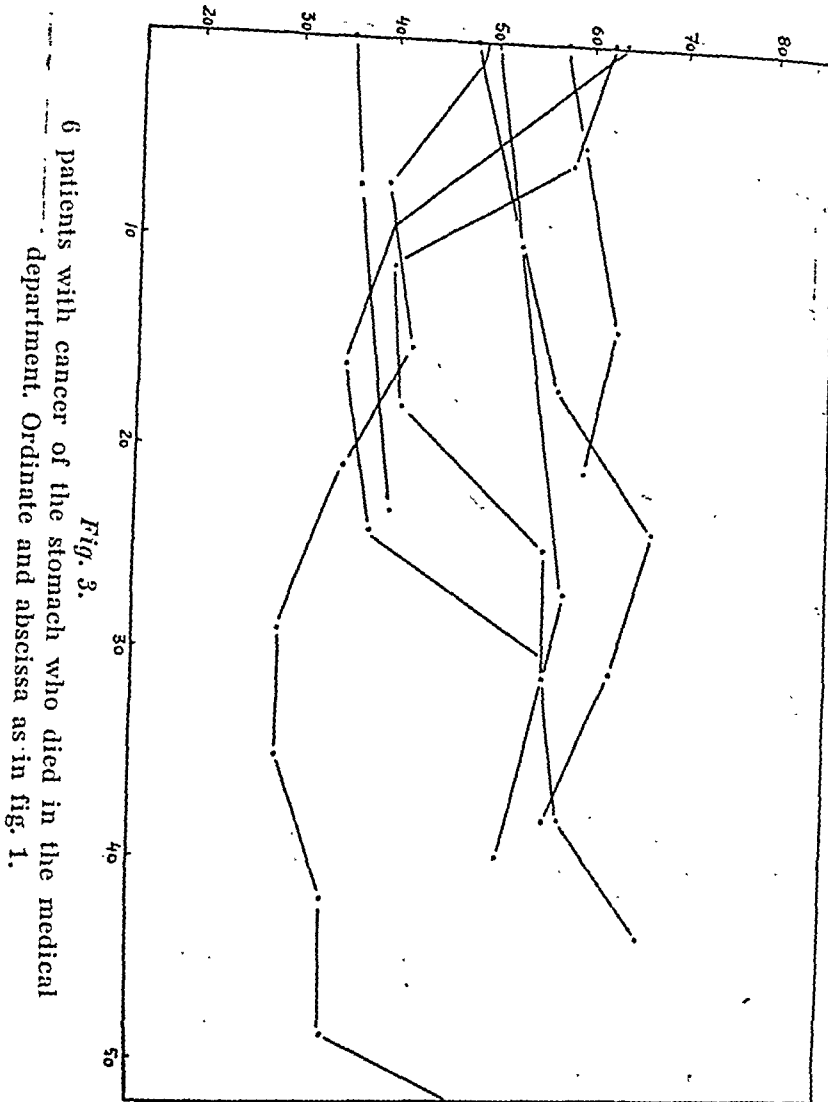


Fig. 3.  
6 patients with cancer of the stomach who died in the medical department. Ordinate and abscissa as in fig. 1.

### *Mechanism of Regeneration.*

Probably, the regeneration in cancer is due to an increased production of erythrocytes. We have seen reticulocyte counts as high as 15 percent in these patients. There is one point, however, which I have not seen mentioned in the literature about anaemia in cancer: many of these patients, no doubt, are very much exsiccated. High percentages of haemoglobin may quite often occur. Ehrström and Tötterman attribute this phen-

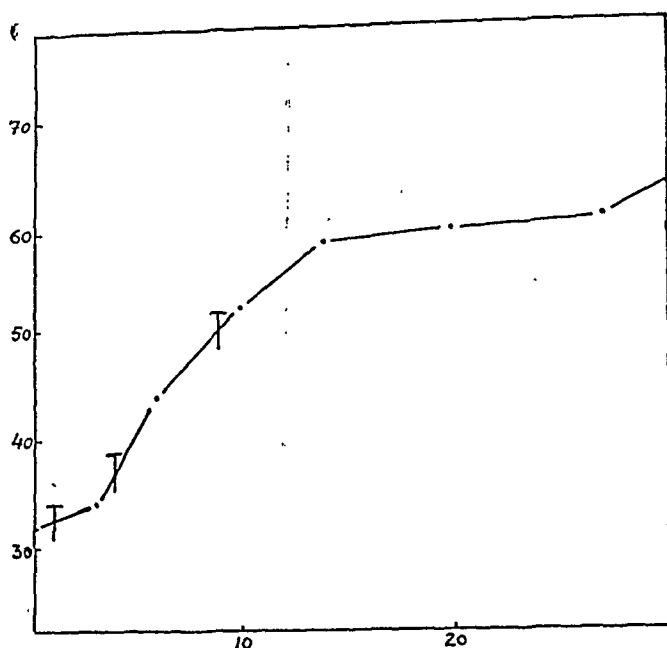


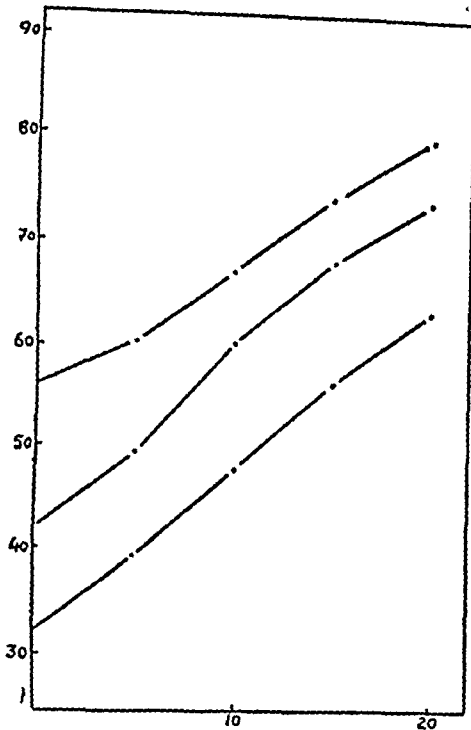
Fig. 4.

Patient with cancer of the stomach (inoperable) who had three transfusions of blood (marked T). Ordinate and abscissa as in fig. 1.

omenon to stimulation of the blood-supporting apparatus of the stomach. I am more inclined to think that they are due to exsiccation, as they generally fall to a lower level when the patient is cared for. Some of the very sudden rises in haemoglobin may also be influenced by the changes in body-water.

### Summary.

137 pts with cancer of the stomach and 18 pts with cancer of the colon have been investigated. The pts have been divided into groups: resection, inoperability and death. Haemoglobin percentage has been somewhat lower in those pts who died but the difference has not been great enough to aid the prognosis. Some patients regenerate their haemoglobin as well as patients with haematemesis or melaena from peptic ulcer. But in most pts, the regeneration is much slower. This — together with bleeding — in some cases where X-ray-examination has failed, has lead to an explorative laparotomy and resection of a cancer.



*Fig. 5.*  
Composite curves of haemoglobin regeneration in 16 pt.s with haematemesis or melaena from peptic ulcer. Ordinate and abscissa as in fig. 1.

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## OSTEOPOROSIS OF THE VERTEBRAL COLUMN

*(Report of a Case.)*

By

*Eigil Hess Thaysen.*

There can hardly be any doubt that osteoporosis of the vertebral column still remains relatively unnoticed even though this lesion is not very rare, being mentioned fairly often in the literature. For instance, since 1938 no less than six fairly large series of such cases have been described, 1, 2, 3, 4, 5, 8.

The case to be reported here is of interest because it illustrates how this affection of the back may be misinterpreted in spite of the characteristic clinical features, and also because it demonstrates the favorable effect that often may be obtained with calcium and vitamin D medication.

The patient is a man, aged 60, baker by trade, who stated that he always had taken an ordinary mixed diet and never had any dyspeptic complaints. At the age of 34, in a traffic accident, »something broke« in his right shoulder. Nearly one year later he had transitory pains over the loins, and at that time, he says, roentgenograms showed some »projections of cartilage« on the spinal column. Otherwise his health had been very good — in particular, he had had no backache — until the age of 55, when he suddenly had a severe attack of pain over the loins. It commenced with, his being unable to get out of bed one morning, and he could not straighten his back because of »cramping knots«. As his condition did not improve under bed-rest, he first applied to an out-patient clinic, which he went to for 5 months, in the winter of 1943—44. X-ray examination of the lumbar column showed (Fig. 1,a) halisteresis with marginal osteophytes and commencing »fish vertebral formation« i. e. ballooned disks and compressed vertebral bodies. Further, arthrosis of both acromioclavicular joints and



Fig. 1 a. (1943) Diffuse halisteresis and commencing "fish vertebral" formation of the lumbar column. I indicates first lumbar vertebra.

left shoulder was found. Under the diagnosis of chronic polyarthritis the patient was first given X-ray treatment, later mud-packs, massage and arc-light radiation. As these measures proved of no particular benefit, the treatment was continued in a massage clinic for some months, sucking cups being applied, to no avail. After this, he was told that he was too old for any favorable result.

In the meantime, on account of the intense backache, the patient had to stop work altogether and sell his shop. In despair he now submitted to a chiropractor's treatment for 3 months, under which the pain in the back subsided so much that he was able again to commence working. A few months later, however, he was just as bad off as before, and since he has been troubled with the backache continuously and unable to



Fig. 1 b. (1946) Same picture as in figure 1 a.

work. For a while a new attempt, though futile, massage, arc-light radiation and Russian baths. Then, in spring 1946, the patient was hospitalized for one month. This time the diagnosis was spondylosis deformans and myoses variaae. In the case record of the patient it says that the vertebral column was fixed, with slight dorsal kyphosis and effacement of the lumbar lordosis. Attempts at movements gave intense pain, and the patient had great difficulty in sitting up in bed. Roentgenography of the dorsolumbar column (Fig. 1, b) showed pronounced diffuse atrophy of the bones and moderate spondylosis. The vertebrae were hourglass-shaped, especially in the lumbar part of the column, but there was no fracture. Also the pelvis showed some halisteresis, but no deformity. X-ray diagnosis: Osteomalacia? The hemoglobin percentage, sedimenta-



Fig. 1 c. (1947) Compression fracture of the first lumbar vertebra. Tendency to bridging osteophytes.

tion rate and urine analysis were normal. The patient was given X-ray treatment and physiotherapy, which was continued after his discharge — without any demonstrable improvement.

In June 1947 the patient was referred to the *Medical Out-patient Clinic of the Rigshospital* for thoracic myoses and neuralgia (Record No. 2285/47).

On admission the patient complained of intense pain over the loins, radiating out in the flank and forwards over the chest, where it was of neuralgic character. There were no pains or paresthesias of the extremities.

The patient is large, robust and a little obese, otherwise of normal appearance. The entire spinal column is strongly fixed,

with the mobility reduced in all directions. The trunk is somewhat sunken, and the extremities appear relatively long. There is moderate dorsal kyphosis, while the loin is short and flat. There are transverse folds of adipose tissue in the flanks. There is no direct or indirect tenderness of the entire spinal column.

*Roentgenography* of the dorsolumbar column (Fig. 1,c) shows distinct halisteresis with pseudosclerotic edges of the vertebral bodies. In several parts, especially in the lumbar, the vertebrae look like »fish bones«. In addition, there is rather pronounced spondylitis deformans with tendency to bridging osteophytes. In the upper margin of the 5th thoracic and the 1st lumbar vertebrae there are distinct breaks in the continuity, signifying a compression fracture in the places. X-ray diagnosis: Osteomalacia.

The sedimentation rate, serum protein, serum calcium and phosphatase are normal.

Clinically the lesion is diagnosed as osteoporosis of the vertebral column, and treatment is instituted with calcii phosphas praecipitatus (1 level teaspoonful  $\times$  3 daily) and calci ferol (20 drops  $\times$  3 daily), corresponding to a little over 10,000 I. U. of vitamin D<sub>2</sub> daily.

As early as one week later the patient claims that he is getting a little better, taking now less analgetic (previously 6 phenacetyl codein tablets daily) and being able to lie on his back — something he has not been able to do for many years. Four months later he sends the clinic a letter, saying: »I have commenced working again. I still have some discomfort when I get tired, but after resting a while it is all gone again. Now I hardly ever take any pills (analgetic) ....«

### *Epicrisis:*

A baker, aged 55, has a sudden onset of intense pain over the loins. In spite of X-ray treatment and protracted energetic physiotherapy, this pain persists through four years, disabling the patient to such an extent that he has to give up his work. X-ray examination in the first and last two years of illness shows pronounced progressive halisteresis, especially in the lower part of the vertebral column.

The outline of the vertebral bodies appears typically sharp, with accentuated concavity proximally and distally (>fish vertebrae) and successively also a couple of compression fractures. Chemical analysis of the blood reveals no abnormality. Under the diagnosis osteoporosis of the vertebral column, the patient is treated with calcium and vitamin D — with very good effect.

### *Comments.*

In the course of time a great number of works have been published on halisteresis of the spinal column with severe backache. This patient material, however, is rather heterogeneous, comprising cases of manifest osteomalacia due to a negative calcium balance — brought about, for instance, by starvation, steatorrhea, pregnancy, or chronic uremia — as well as cases of osteoporosis due to endocrine disturbances involving the pituitary, parathyroids or thyroid. Besides these two groups of lesions, moreover, there are a considerable number of cases in which no definite cause of the halisteresis could be demonstrated, and this group constitutes a clinically well-defined entity, whereas the views concerning the etiology and pathogenesis of the lesion have been strongly divergent.

Like *Meulengracht* 5, several authors think that here we are dealing with a sort of senile osteomalacia, appearing on the basis of greatly protracted dietary deficiency, disturbances of gastrointestinal absorption, or both forms of insufficiency. This view may find support in the favorable results often obtained with calcium and vitamin D therapy 1, 2, 6, 9.

Other authors think that here we are faced by a senile or presenile form of osteoporosis. But this expression is not satisfactory, as the average age of the patients is about 60 years, and many of them are considerably younger.

In a fairly comprehensive review *Burrows & Graham* 3, take no decisive stand concerning the problem but speak of osteoporosis of unknown origin. *Albright* and collaborators 1, designate the lesion as post-menopausal osteoporosis and think it is attributable to the cessation of estrin production. A point in favor of this view is the fact that the affection preferably appears in women past the climacteric, and also that such

patients treated with estrogenic are said to show a pronounced retention of calcium and phosphorus. But Albright's theory offers no adequate explanation of the occurrence of the disease in men and in younger women with normal menstruation.

A few times the osseous tissue has been examined post mortem, and then it proved to be of osteoporotic character. So it is not very likely that in this disease we are dealing with osteomalacia proper. Nevertheless, *Meulengracht* 5 undoubtedly is right in assigning a certain etiological role in the appearance of the lesion to calcium and vitamin D deficiency. This seems evident from the aforementioned subjective improvement often observed in the patients given calcium and vitamin D. Furthermore, recently a reexamination of patients from *Meulengracht's* clinic has shown that the progressive decalcification of the spinal column appears to stop on administration of these substances. In this connection it is of interest that *Owen* 7 has demonstrated that the calcium requirement is the same for the relatively old organism as for the young and growing individual.

Even though the halisteresis, on the other hand, never decreases noticeably under the given treatment, the above data still indicate that when calcium and vitamin D are readily accessible to the organism, they either have a favorable influence on the osteoblast function, or they inhibit the bone absorption by the osteoclasts.

There has been some doubt as to the proper dosage of vitamin D<sub>2</sub>. Considering that in our patient presumably we are dealing with an instance of osteoporosis, I would take about 10,000 I.U. vitamin D<sub>2</sub> daily to be a rather suitable dosage, especially as this dose gives no calcinosis.

The case here reported is very characteristic, and in such cases even the history and inspection of the patient give some suspicion about the presence of this lesion. As to the X-ray findings, it will suffice here to remind that *Meulengracht* has designated them very aptly as resembling poor roentgenograms. As a matter of fact, the more comprehensive papers cited above give a thorough description of the clinical aspects of the disease and elucidate also the differential-diagnostic problems involved.

This casuistic report, I hope, will serve further to establish how important it is in similar cases to keep the possibility of

osteoporosis of the spine in mind because calcium and vitamin D therapy is a simple and comparatively effective measure in dealing with this sometimes very disabling lesion, and also because the treatment otherwise usually resorted to in cases of intense backache most often will fail here. Finally, X-ray treatment probably will be contraindicated here, as this affection involves an osteoporotic process.

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## A CLINICAL STUDY OF ANTI-STREPTOLYSIN AND ANTI-STAPHYLOLYSIN TITRES IN ACUTE PLEURISY

By

*Alf Westergren, M. D.*

In the present paper a more comprehensive account will be given of investigations, some principal features of which have successively been preliminarily reported on various occasions during the years 1943—1946. (19, 20, 23, 24.)

The material now comprises 534 cases of acute pleurisy which, according to the prevailing opinion, is more or less obviously tuberculous in origin. In every one of the cases the antistreptolysin titre (AST) was estimated within three and a half months after appearance of the first symptoms of pleurisy, and among these antistaphylolysin titration (AS<sub>t</sub>a) was in addition carried out in 340 cases. The sero-bacteriological work was performed in co-operation with the State Bacteriological Laboratory under the supervision of Dr. S. Löfgren and Professor Th. Packalén. During certain periods also special bacteriological examinations were made, the results of which revealed a fairly close general relation to the serum titres, (2, 3, 7, 11, 15.) A proportion of the cases examined in this way are included in the following series, but it will not be possible to give the bacteriological findings for more than a few of them.

### *Followed-up cases.*

Practically all cases were examined serologically more than once, and nearly a hundred with at least ten tests during more than one year. The following twenty-two cases were selected to show different types and variations of the AST and AS<sub>t</sub>a curves.<sup>1)</sup>

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<sup>1)</sup> *Abbreviations used in the graphs.*

*Ab.* = Abscess. *B* 1, 2, 3, etc. (below) = Bacteriological examination (throat swab, etc.). *C.* = "Cold" symptoms. *D.* = Dental symp-

*Case 1.* (R.P. 24 years) may be regarded as a sub-primary pleurisy. Symptoms since about April 6th. T.C. on April 18th: 3,200 c.c. Very slight parenchymal affection. Favourable course (as far as known in May 1946).

The AST in first test (April 17th, 1945) 200 units, rising to 600 in two months and dropping to 100—140. Some increase after completed pneumothorax treatment, together with "cold" symptoms, in February 1946. The AS<sub>t</sub> in first month about 1,4 international anti- $\alpha$ -staphylolysin units, rapidly rising to about 6,0 and then gradually dropping to 0,4.

This case can be considered a typical average one where both titres are influenced.

*Case 2.* (R.R. 32 years.) Dental troubles and "cold" symptoms in February—March. Slight chest pain since April. Ill with fever and clinical signs of pleurisy on May 6th. T.C. 2,000 c.c. Hilar and slight perihilar affections.

A recent acute pleurisy indicated by the S.R. curve. The AST nearly the same as in Case 1, but here the titre was reduced to 60—80 units about one year after the acute pleurisy. The AS<sub>t</sub> more influenced than in Case 1.

*Case 3.* (F.S. 41 years.) Symptoms since about February 15th. T.C. 3,000 c.c. Moderate pulmonary processes of a chronic type, showing some slight progression. Very bad dental state.

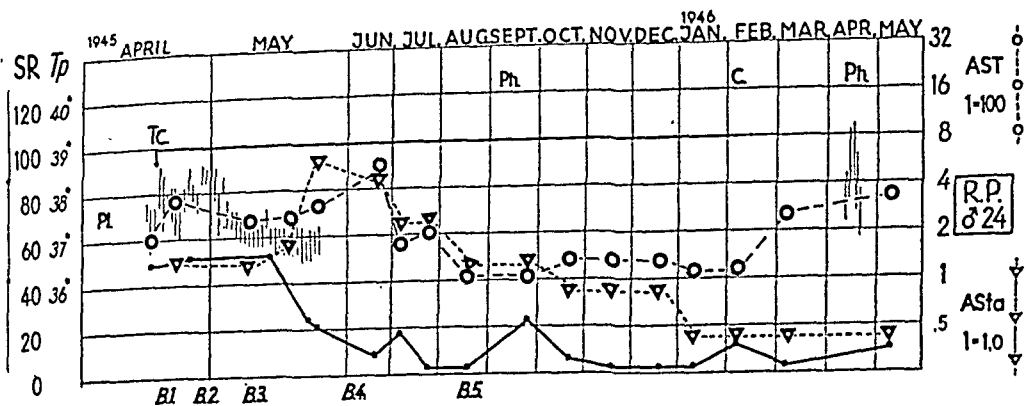
The AST in first test low (70), gradually rising to 450, and afterwards showing fairly regular variations about 100—360—100. The AS<sub>t</sub> rising from 1,7 to about 4,0 in three months, and then dropping again to nearly the same level as in the first tests.

*Case 4.* (M.L. 34 years.) X-ray from 1943 showed some hilar affection and a very slight apical lesion on the side of acute pleurisy in 1945 (somewhat more distinctly visible in 1946, after completed pneumothorax treatment). — Marked dental troubles in February—March, 1945. Slight chest pain since end of April. X-ray on May 5th showed the hilar density somewhat enhanced but still no signs of pleurisy. Fell ill on May 9th. T.C. 2,000 c.c.

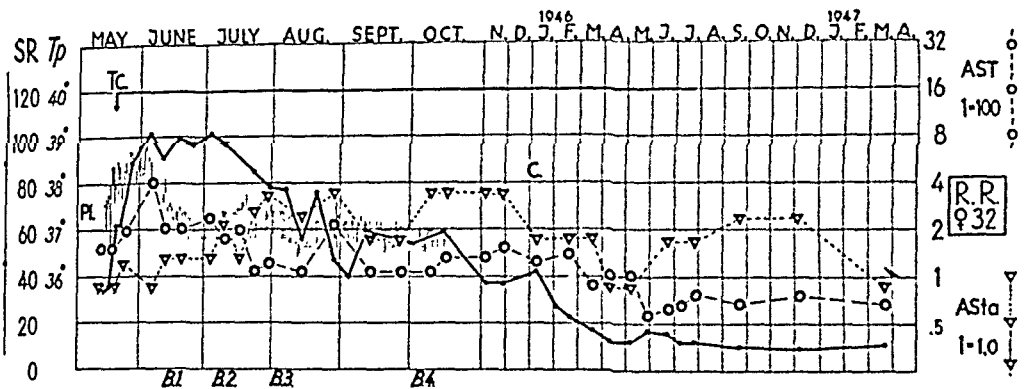
The AST during first month 60—70, than rising for about 5

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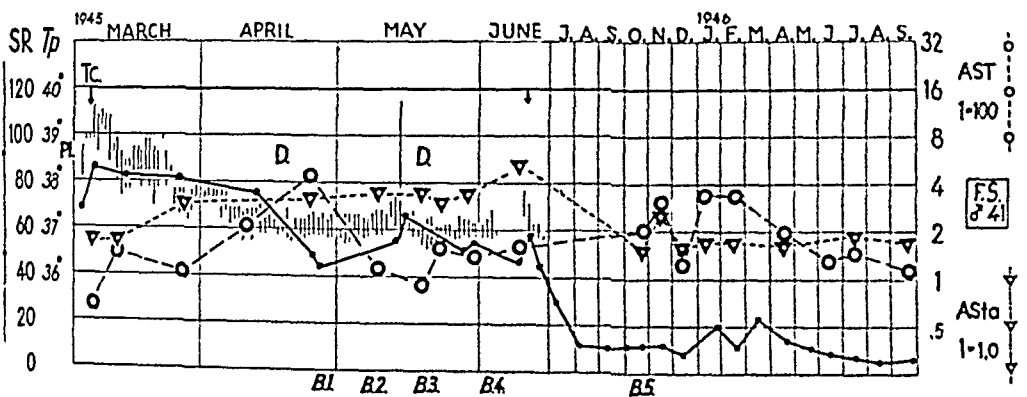
toms or operations. *Emp.* = Empyema. *E.N.* = Erythema nodosum. *G.* = Gall affection. *J.* = Joint symptoms. *Men.* = Meningitis. *Mil.* = Miliary tuberculosis. *Perit.* = Peritonitis. *Perf.* = Perforation. *Ph.* = Acute Pharyngitis or Angina. *Pl.* = Acute Pleurisy. *pl.* = Pleural effusion in pneumothorax. *T.C.* = Thoracocentesis. *T.E.* = Tonsillectomy. — A coarse line (after T.C.) indicates that artificial pneumothorax was maintained (Cp. 18, 19).



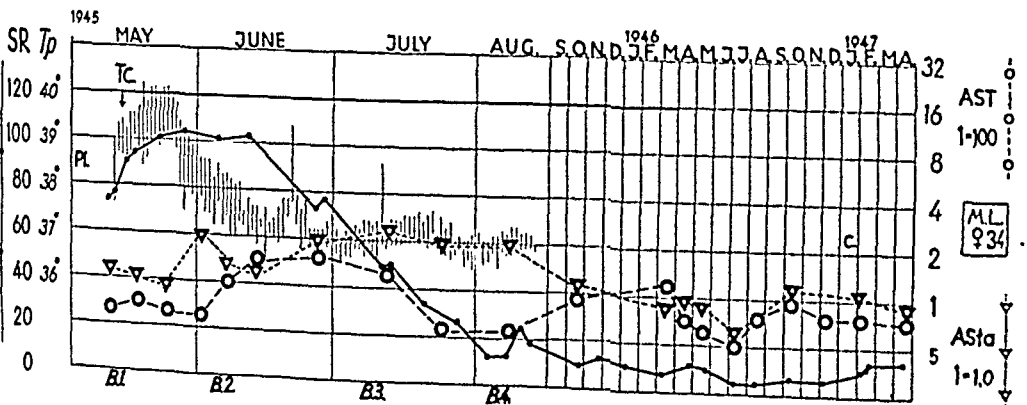
Case 1.



Case 2.



Case 3.



Case 4.

weeks, but only to about 150, and afterwards dropping. The ASTa of very similar course, but on a comparatively higher level.

Notwithstanding the AST in this case never reaching the "pathologic" limit of 200 units, it seems evident that some changes in the activity of  $\beta$ -hemolytic streptococci (as well as the yellow staphylococci) have occurred during this period of observation.

*Case 5.* (A. B. 26 years.) Erythema nodosum in March, 1945 with some bilateral hilar density. Distinctive tonsillar troubles in April—June. Acute pleurisy in June, with relapse in August.

In this case it may be mentioned that the bacteriological throat-swabs, B 1 to B 4, before tonsillectomy in November showed abundant findings of both  $\beta$ -hemolytic streptococci and yellow staphylococci, but the examinations after tonsillectomy, B 7 and B 8, were negative in both respects. The titre curves, however, hardly show any influence of the tonsillectomy.

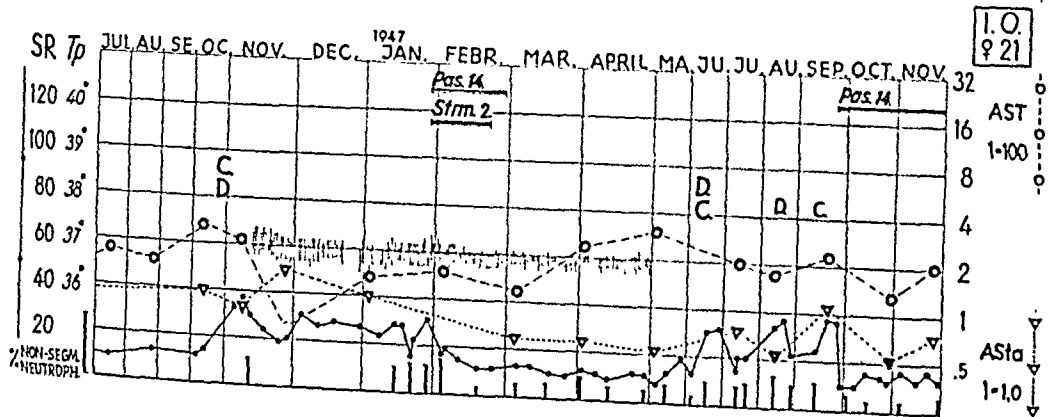
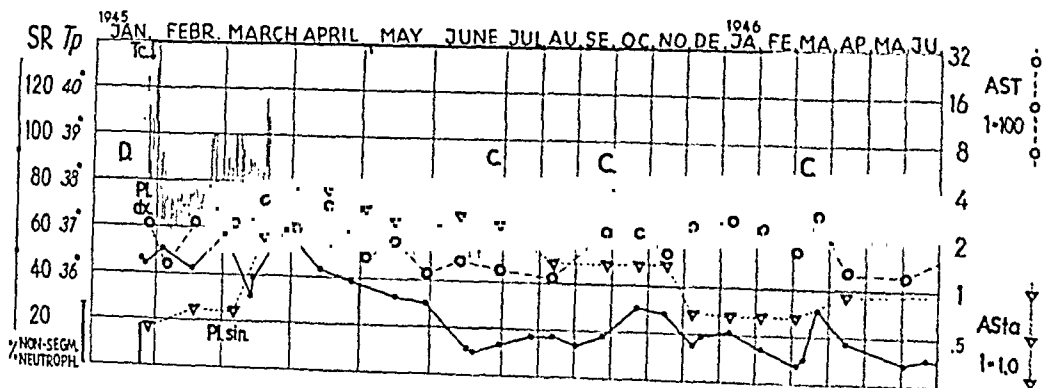
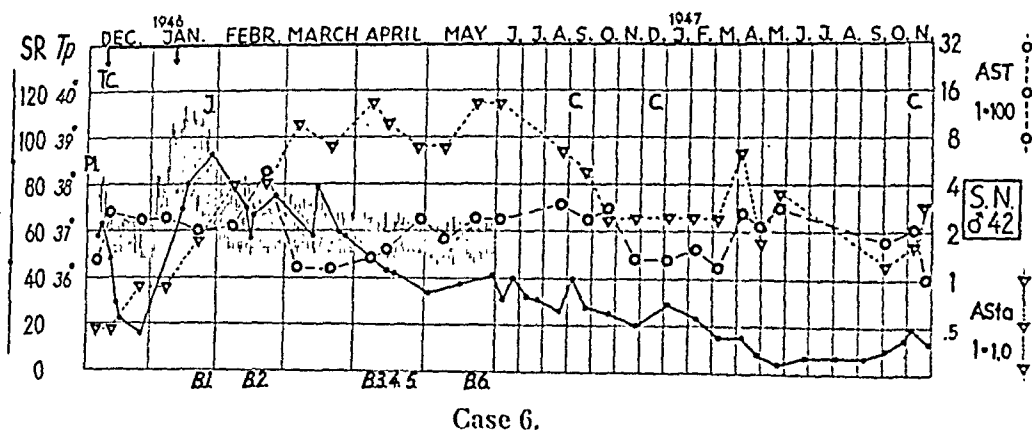
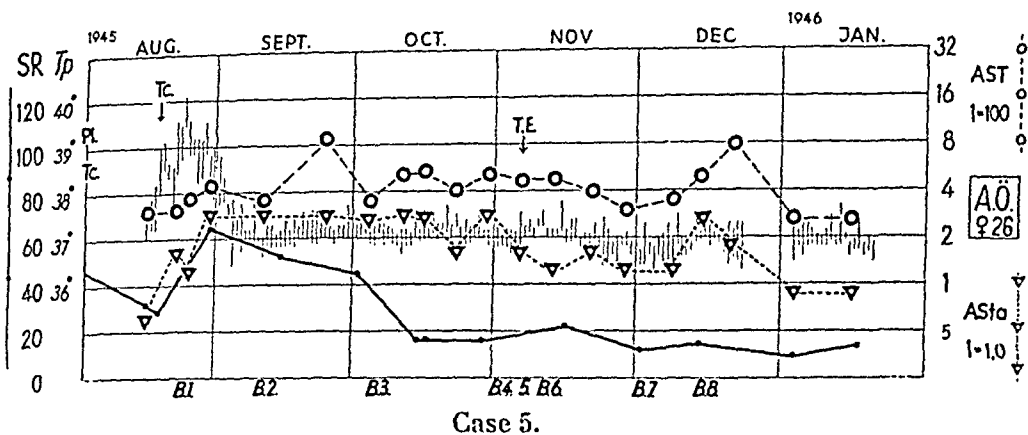
The AST on a fairly high level (300—800). The ASTa showing a typical early rise and later on decreases.

*Case 6.* (S. N. 42 years.) Small chronic pulmonary lesions known since 1942. Fever and chest pain about November 20th, film on the 22th showed no signs of pleurisy. In December a rather slight pleural effusion appeared, with relapse and increased exudation in January—March. (Altogether, about 5,000 c.c. was removed.)

The AST about 200 with regular variations, most probably not due to technical imperfections. The ASTa in this case showed a particularly marked rise from 0,9 to no less than 14 units and then gradually dropped, but was still on a patologic level in November, 1947.

*Case 7.* (I. O. 21 years.) After a period of dental and throat disorders in December, 1944 and January, 1945 acute right pleurisy on January 24th. T. C. 1,100 c.c. Towards the end of February a slight left pleurisy developed (no T. C. and pneumothorax could be performed on this side). On the first X-ray no parenchymal lesions were found, but during 1945—1947 a moderate left pulmonary process developed, with suspicious cavities. In 1947 treatment with Para-amino-salicylic acid (PAS) combined with Streptomycin (Strm.), and only PAS, respectively, with favourable results (Cp. S. R. curve and decrease of the non-segmented leucocytes).

The AST in practically all the thirty-nine tests between 100 and 300, with rather small but perhaps not quite insignificant variations. The ASTa shows very marked rise from 0,4 to 3,8 and then a slow but rather steady descent.



*Case 8.* (M.D. 28 years.) Acute pleurisy in May, 1945, and relapse towards the end of July. T.C. only 120 c.c. Small apical affection on the same side.

The AST shows typical rise from 50 to about 500, in this case particularly related to the relapse of pleurisy, with thoracocentesis, but also to frank throat and dental symptoms (Cp. S.R. curve). AS<sub>t</sub>a evenly decreasing from 3,0 to 0,9. — No influence on the titres by tonsillectomy in December.

*Case 9.* (U.F. 20 years.) A routine film in January, 1945, had only shown an old left central affection of a healed type. Costal stitch in March—April. Fell ill in July with slight left pleurisy (and later also on the opposite side). Some bilateral parenchymal processes of a rather acute type. At first marked improvement but between May and August, 1947, moderate progression. (At that time no pleurisy.)

The AST rising from about 200 to 600—400. The AS<sub>t</sub>a evidently high at an early stage, soon abating to about 0,9.

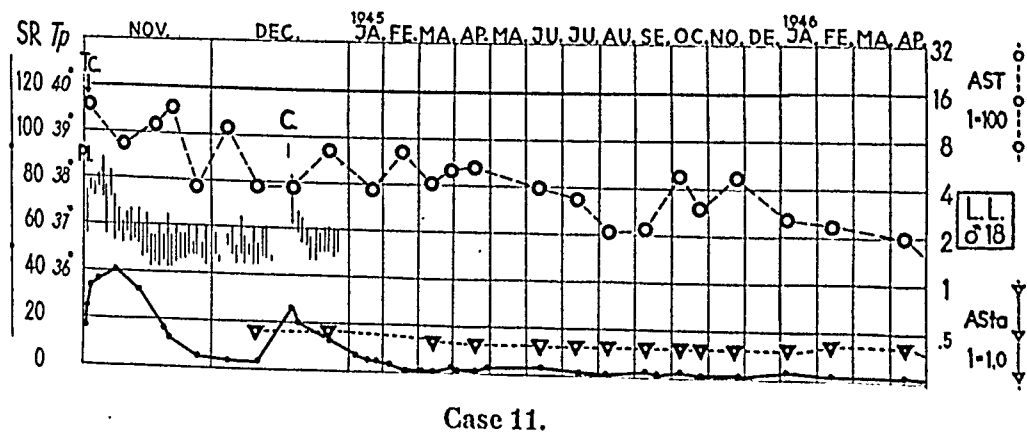
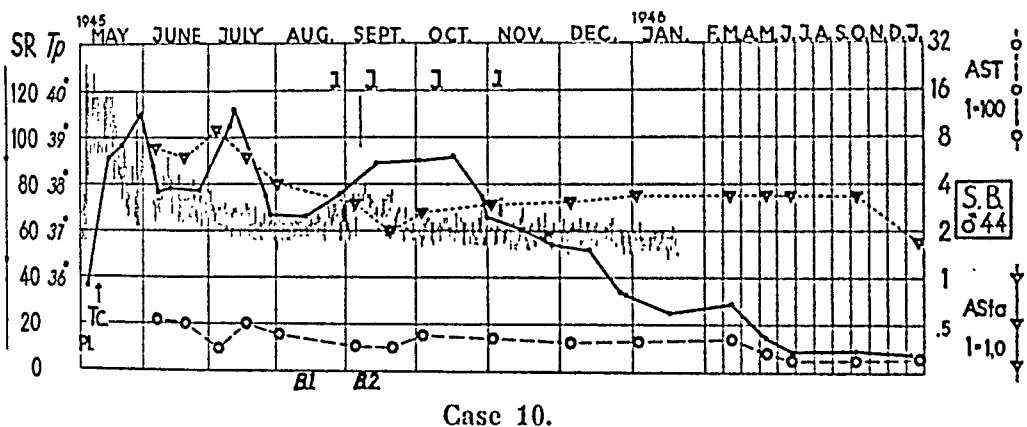
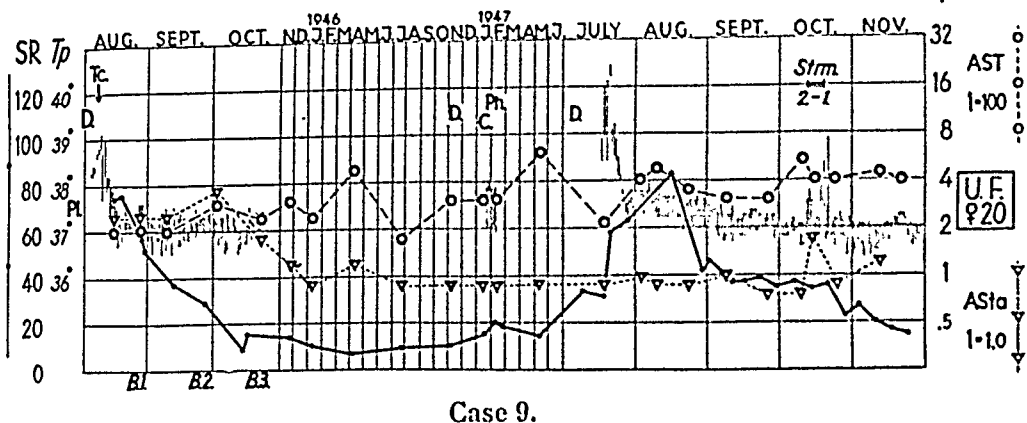
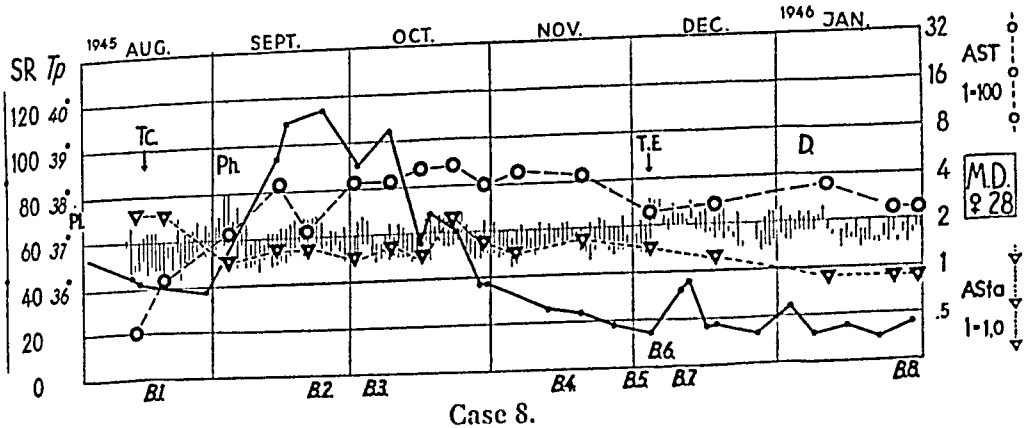
*Case 10.* (S.B. 44 years.) Quite acute pleurisy on May 1st. T.C. 200 c.c. Fairly slight pulmonar affection of a chronic type. (Had subsided in December, 1947.) During a fever period in August—November rather severe joint symptoms of polyarthritis type.

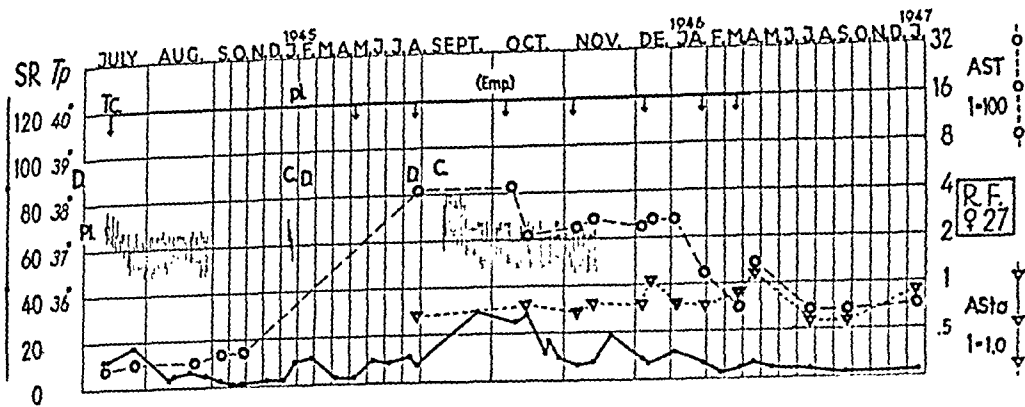
AST consistantly low but showing a tendency towards decreasing (from about 50 to 20). AS<sub>t</sub>a initially very high (about 8,0), gradually dropping, but only to 1,8.

*Case 11.* (L.L. 18 years.) Erythema nodosum in May, 1943, with hilar density, chiefly left, with alternating progression and regression during 1943—1944. A routine examination in October, 1944, revealed a comparatively small left pleurisy, soon increased. T.C. 800 c.c.

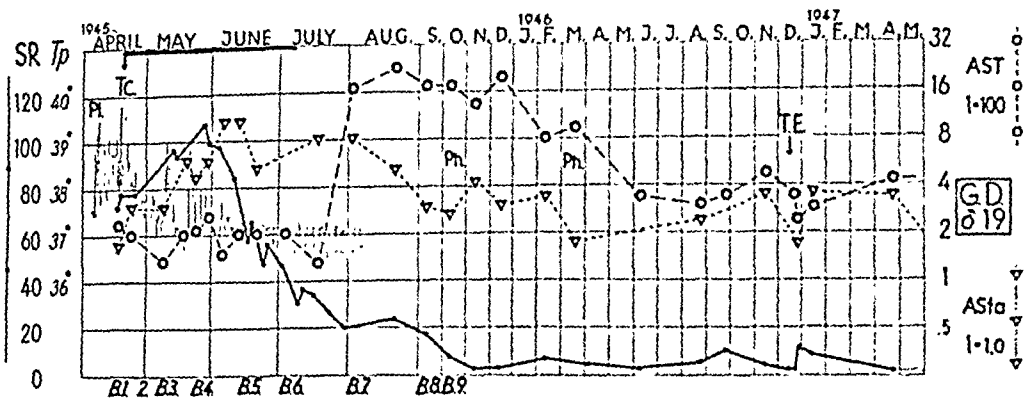
AST very high, about 1,200, gradually diminishing but after one year still about 400. AS<sub>t</sub>a consistantly below 0,5.

The cases 10 and 11 very clearly illustrate similar types of reacting, with the two titres changing parts.

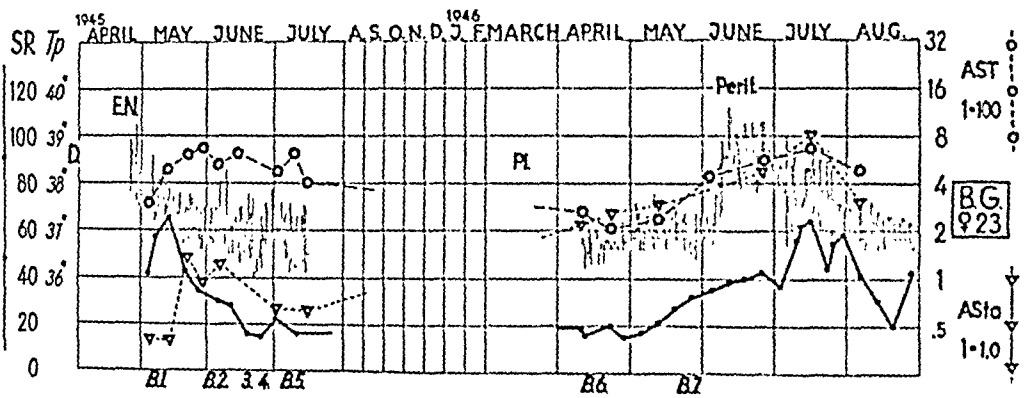




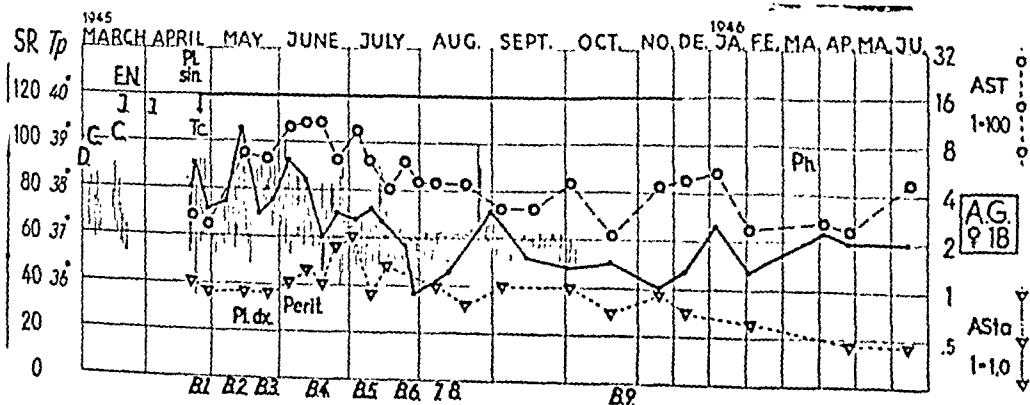
Case 12.



Case 13.



Case 14.



Case 15.

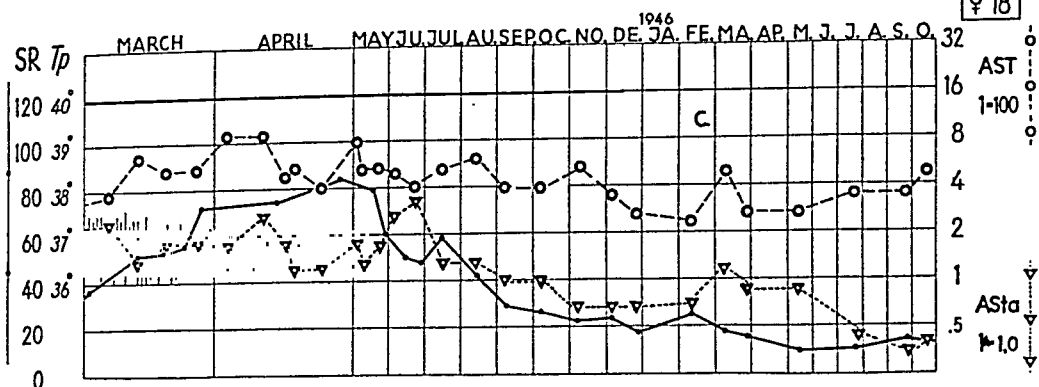
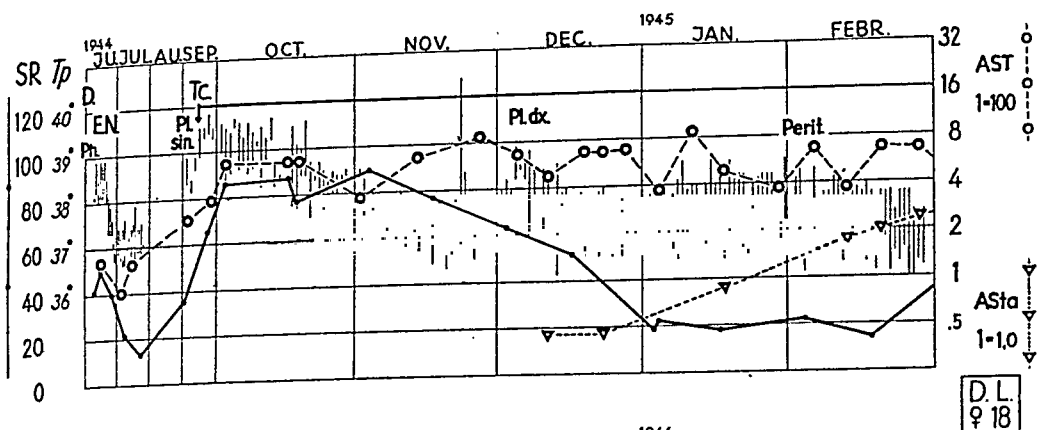
c.c. In May—June a slight pleurisy on the other side, and also peritonitis. Pulmonary processes had almost completely disappeared after pneumothorax treatment (X-ray in 1946 nearly normal) but towards the end of 1947 progression has taken place.

Case 15, besides, e. g., Case 1 represents a typical behaviour of both titres.

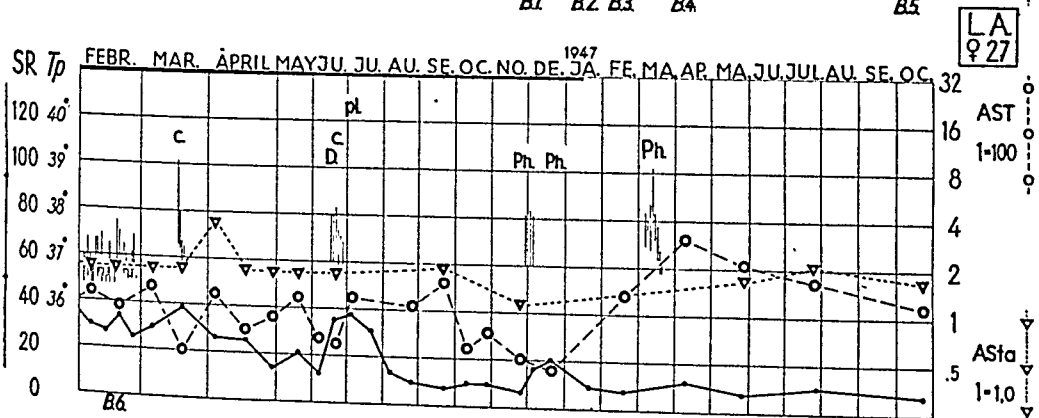
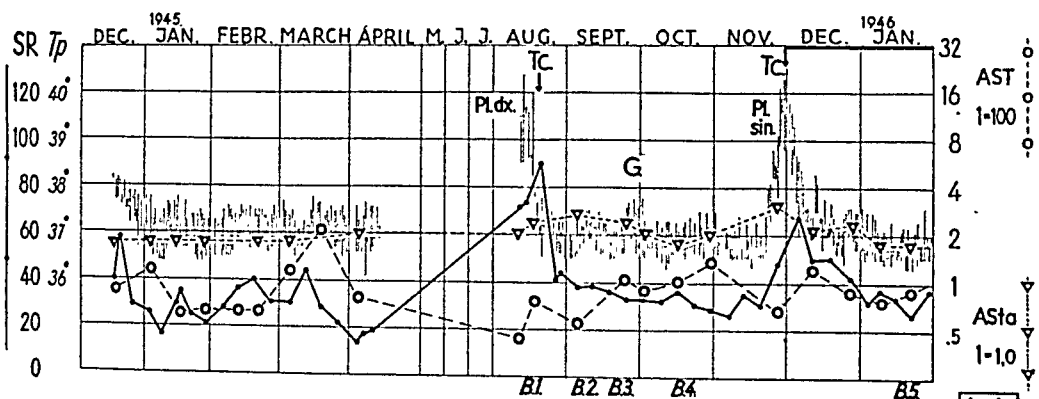
*Case 16.* (D. L. 18 years.) Nodal fever in June and acute pleurisy towards the end of September. Primary parenchymal process of the left lung. No relapse of the left pleural effusion after T. C. in September (1,400 c.c.). Satisfactory pneumothorax. During December, 1944—February, 1945 seriously ill (the low S. R. should be interpreted as an anergic manifestation) with pleurisy on the opposite side and peritonitis. Very marked improvement afterwards.

The AST, contrary to Case 14, was here only slightly elevated (about 150) during the nodal fever, but on the first day of pleurisy the titre was 300, and rates between 400 and 800 persisted for more than one year. The AS<sub>1</sub>a rising from 0.4 in December, 1944, to about 2.0, and was gradually subsiding to definitely normal values after one and a half year.

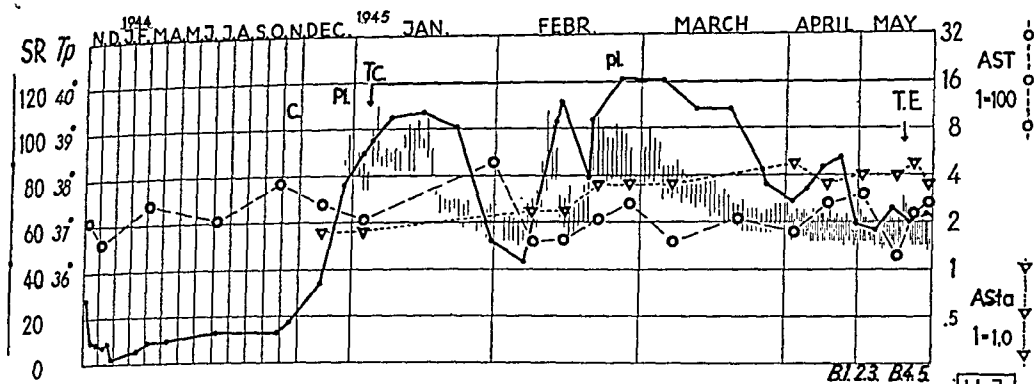
*Case 17.* (L. A. 17 years.) In December, 1944, left chest pain. Bilateral central and perihilar affections, chiefly left, were discovered, showing some progression and then regression. (No pleurisy.) From July, 1945 onwards right pleurisy. T. C. August, 21st (only 250 c.c.). In September gall-stone affection with jaundice. Subsequently a certain parenchymal progression on the left side, and in November a pleurisy suddenly developed here. T. C. 300 c.c. Fairly satisfactory left pneumothorax during 14 months. Favourable course up to the present moment.



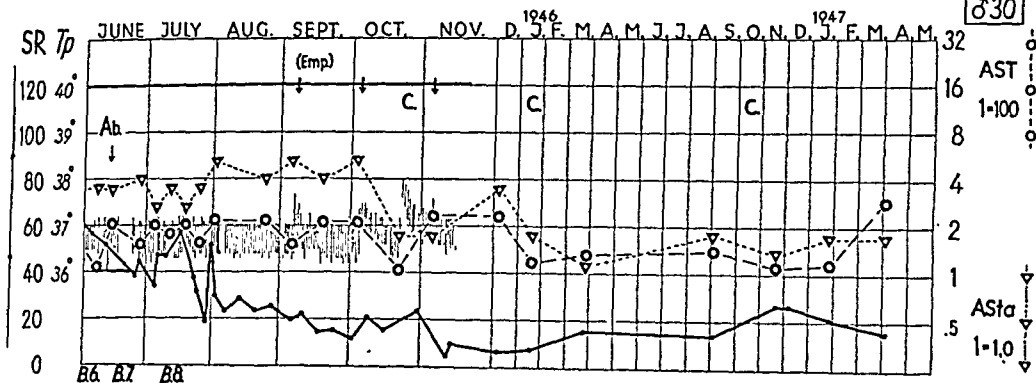
Case 16.



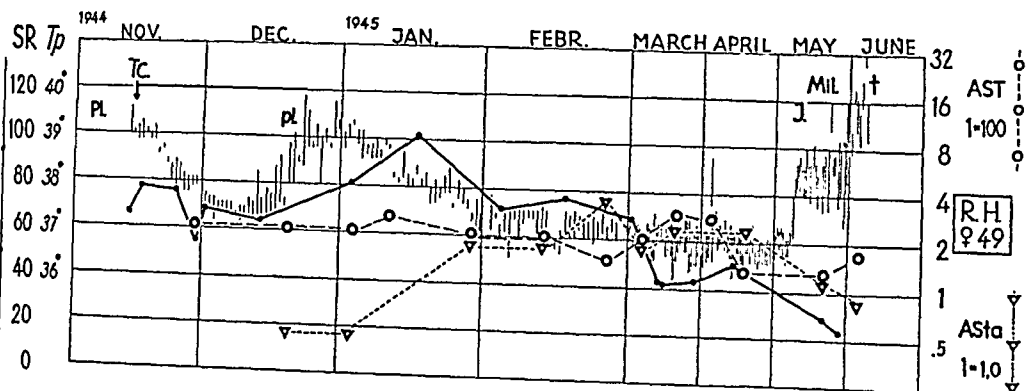
Case 17.



H.J.  
δ30

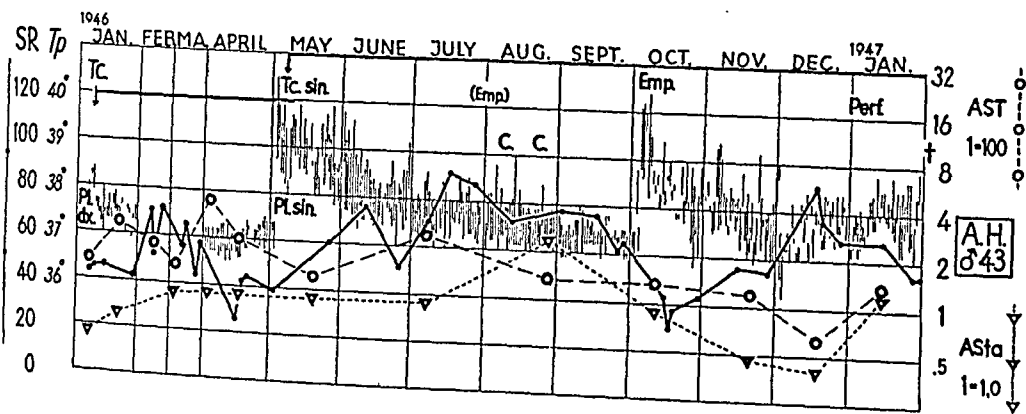


Case 18.



R.H.  
949

Case 19.



A.H.  
δ43

Case 20.

*Case 21.* (R. S. 34 years.) Acute left pleurisy about June 12th. Moderate parenchymal processes of chronic type. At first satisfactory improvement (Cp. S.R. curve), but in October acute pleurisy on the opposite side supervened, together with progression of the pulmonary processes. Peritonitis, miliary tuberculosis and meningitis.

*Case 22.* (C. G. 20 years.) After some "cold" symptoms in January, 1945, a central affection of primary type was demonstrated in May, with a certain consequent progress. Pleurisy from beginning of September, soon abating (T.C. 200 c.c.). Slight transitory abdominal symptoms about December 1st. From end of February onwards a tuberculous peritonitis of malignant type.

Among these fatal Cases 19—22, the AST was found somewhat above 200 in the Cases 19, 20 and 22, but in Case 21 it was very low. The AS<sub>t</sub>a in Case 19, 20 and 21 showed a considerable rise from low rates but not until a rather late stage, in Case 22 it was initially high.

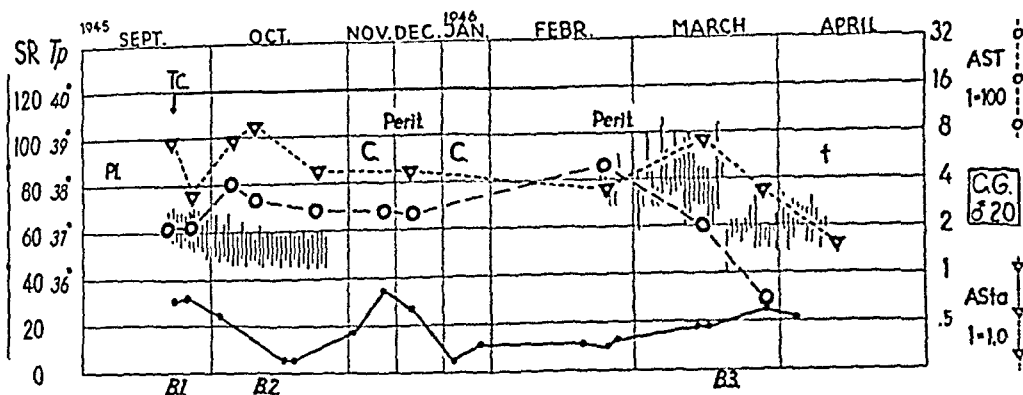
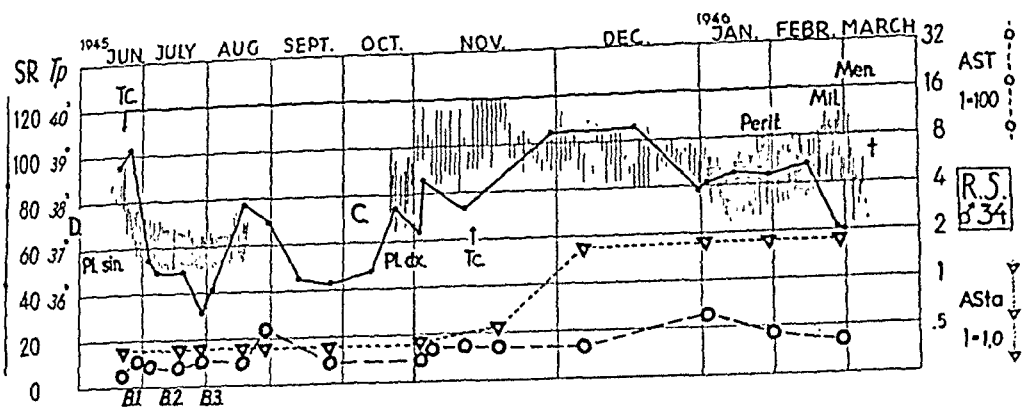
Especially in Case 22, but also in the Cases 19 and 20, a drop will be noted in either titre curve running parallel to a definite decline of the general condition. — This phenomenon is also evidenced by the behaviour of the S.R. (which to a certain extent even applies to Case 22).

#### *Incidence of elevated titres.*

In Table 1. the cases are divided into groups in respect of tuberculous pulmonary lesions (at the time of the recent acute pleurisy) and manifestly progressive tuberculosis (during the first year), respectively.

The application of the principles of classification may be illustrated by mentioning that among the followed-up cases presented above, the Cases 1, 2, 4, 5, 6, 7, 8, 10, 11, 12, 13, 14, 16, 20 and 22 were referred to the group without or with but very slight pulmonary processes, and the Cases 7, 9, 14, 15, 16, 17 and 19—22 to the groups of progressive tuberculosis.

The conception of "primary" (or, in most cases, better sub-primary) pleurisy, indicating that the pleural affection has developed in connection with a primary tuberculosis infection, seems to be somewhat vaguely founded, and rather much misused. In a couple of cases of the present material such a designation



should of course be fully adequate (most of these cases — not all — are to be found in the first main group of the table) but a differentiation from “post-primary” pleurisy has proved to be much more precarious than the conception of the two main groups (without or with very slight parenchymal affections, and pulmonary tuberculosis cases, respectively) applied in Table 1. The cases with certain or probable primary pleurisy seem by no means to show a lower incidence of elevated AST than the cases of the first main group of the table (which practically might be termed *initial pleurisy*).

In the table are included the percentages of cases showing rates of over 200 units for the AST, and over 1.0 units for the ASa, respectively (and the standard error of each frequency figure). The figures at the top of every cell indicate the number of cases.

The columns 13 and 14 give the frequency-figures for the entire material. In 341 cases AST was tested within two weeks after the initial symptoms of pleurisy (period a). 36.6 % of

these (i. e. 125 cases) have shown titres of over 200 units during this period. Among the 341 cases ASta was also estimated in 211 cases, 46.4 % (98 cases) showing rates above 1.0 units. On the next line the whole period (A) of three and a half months from the beginning of the pleurisy is referred to. There is a certain rise in both frequency-figures, viz. from 36.6 % to 43.6 % and from 46.4 % to 56.2 % respectively. In period B only the time *after* three and a half months (to one year) is dealt with. The frequency figure for AST is 35.8 % and thus very similar to that of the first two weeks, the ASta figure is 51.7 %, i. e. intermediate between those for the preceding periods.

Let us now for a moment consider only the AST figures. *A conspicuous difference will be noted between the cases without and with pulmonary tuberculosis*, and above all the frequency-figure 49.1 % in all the "pure-pleurisy" cases (cell A 5) as against 29.8 % in the "pulmonary-tuberculosis" cases (cell A 11) should be pointed out particularly.

If attention is paid to the evidently *progressive* cases as compared with the other ones, remarkable differences are likewise to be observed; in the "pure" group (column 1) the three periods carry the frequency-figures of 36.7 %, 43.5 % and 31.3 %, respectively, for the non-progressive cases as against 60.0 %, 72.6 % and 61.1 %, respectively, for the progressive cases (column 3) and in the main group (three and a half months) among the parenchymous cases (A 7 and A 9) the differences as regards progressivity may be considered to be very well-marked. The difference between the cases without appreciable parenchymal affections and the proper pulmonary tuberculosis cases just mentioned is significant among the progressive cases (A 3 with 72.6 % as against A 9 with 44.8 %). In the columns 15 and 17 all the progressive cases can be compared with the non-progressive within larger series.

The highest incidence of elevated AST is 72.6 %, as shown by the cases of progressive tuberculosis in the group of "pure pleurisy", — i. e. cases where, according to general clinical usage, at an early stage of the pleurisy the possible existence of pulmonary lesions is as a rule not observed or even taken into account, — and the lowest is 22.9 % for the non-progres-

	Parench. proc:s 0 to +				Parench. proc:s + +				All non-progress. cases				All progressive cases					
	Progress. Tuberc. O to (+)		+ +		Progress. Tuberc. O to (+)		+ +		All cases		All cases		All non-progress. cases		All progressive cases			
	AST >200	Asta >1,0	AST >200	Asta >1,0	AST >200	Asta >1,0	AST >200	Asta >1,0	AST >200	Asta >1,0	AST >200	Asta >1,0	AST >200	Asta >1,0	AST >200	Asta >1,0		
Column	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
a	Nr.	204	114	40	23	244	137	57	27	17	97	74	341	211	274	171	67	40
	%	367 ±34	404 ±46	600 ±78	522 ±104	406 ±31	423 ±42	229 ±50	544 ±66	370 ±93	529 ±121	541 ±60	366 ±26	464 ±34	332 ±28	450 ±38	507 ±61	525 ±79
A	Nr.	310	185	73	43	383	228	106	80	45	32	112	534	340	416	765	118	75
	%	435 ±28	541 ±37	726 ±52	721 ±68	491 ±26	575 ±33	236 ±41	550 ±56	448 ±74	500 ±88	536 ±47	436 ±21	562 ±27	385 ±24	543 ±30	619 ±45	627 ±56
B	Nr.	197	88	54	23	251	111	57	38	30	23	61	338	172	254	176	84	46
	%	315 ±33	511 ±53	611 ±66	522 ±104	378 ±31	513 ±47	333 ±62	526 ±81	233 ±77	522 ±104	525 ±64	358 ±26	517 ±38	319 ±29	516 ±45	476 ±55	522 ±74

Table 1. Frequency of elevated AST and ASTa in 534 (340) cases of acute tuberculous pleurisy.

sive cases of pulmonary tuberculosis with recently acute pleurisy.

If the AS<sub>t</sub>a rates are considered the frequency-figures in many respects are unlike those shown by the AST. On the whole the frequency figures among the "pure" and "parenchymatous" cases, as opposed to the AST rates, are of a similar magnitude. However, a definite increase of frequency from the first period appears in the non-parenchymatous group (columns 2, 4, 6). *Among the groups of parenchymatous cases* (columns 8, 10, 12) *all the AS<sub>t</sub>a rates are fairly uniform*, or even a slight tendency towards a higher incidence in the first two weeks may be traced (column 10) quite contrary to the behaviour of AST. *The progressive, pure cases show a remarkably high AS<sub>t</sub>a rate already in the first period (a), and still more in period A, but in the parenchymatous cases the relation is even reversed* (Cp. p. 344). — Within the group of pure cases, the AS<sub>t</sub>a variations agree with those of the AST.

Attention might be called to the fact that the details now pointed out demonstrate the frequency figures for the entire material (columns 13, 14) in many respects to be mean values between rather divergent groups. As the material comprises practically all the cases of acute pleurisy treated in the Department during a period of about 4 years, the drawbacks pertaining to the figures in the columns 13 and 14 implicated can be regarded as of relative significance only.

If the data given in the tabular survey are collocated with the experience from individual cases as illustrated by the series presented in the foregoing, it should be borne in mind that the table only gives the frequency of cases with titre values exceeding a certain limit. (As a rule two different tests with rates above the limit have been claimed.) A rise in the AST as, e. g., in the Cases 4, 13 and 15, and in the AS<sub>t</sub>a in the Cases 1, 4, etc., is not at all reflected in the table, nor is a decrease as that of the AST in the same Cases 4, 13 and 15, etc. etc. — *Hence, the frequency figures as indicating increase and decrease of the titres from one of the three periods referred to in the table to another must be rather much blunted.*

Only about half or perhaps two-third of the material was followed-up sufficiently to support any opinion on the true general

incidence of titres changes during the course of acute pleurisy and the following six to twelve months. A thoroughly worked-out analysis of this matter has not been possible. Only a few essentials should be mentioned. *In one-half of the cases, at most, the titres seem to be on approximately the same level all the time, either they were high or low in the first test.* A comparatively stable AST, however, seems to be somewhat more frequent than an immobile AS<sub>t</sub>a. (As regards "parenchymatous" cases without progress more than one half, perhaps two-third, do not seem to change their AST rates much.) A noticeable rise of the AST during the course of the pleurisy is observed at least in about one-fourth of the material, and perhaps somewhat more frequently in "pure" cases with progress. A general decrease seems to occur rather less often than an increase. Considering the AS<sub>t</sub>a an actual rise of the titre rates is more common than an increase in the AST, while decreased AS<sub>t</sub>a rates, on the whole, are apparently less usual. Increased values, followed by a decrease, as shown in several of the cases presented above, in this survey of the material could only be traced in at about one-tenth, but no doubt a much higher incidence will emerge if the cases are followed-up more closely. As regards even slight but typical changes as e.g. those of the AST in Case 4, etc. — not to mention Case 10 — very frequently repeated tests within a large material would be required to obtain a fairly precise conception of this aspect of the problem.

*Incidence of elevated titres after the acute stage of pleurisy.*

So far chiefly the first period of two weeks and the main period of three and a half months have been dealt with. The bottom-line in Table 1 (period B) gives the frequency figures for the following time from the 3½-month point to one year after the onset of the pleurisy. All the fractions of the pure group now show a decrease of the frequency figures of the earlier period, most pronounced as regards the AST — from 49,1 % (A 5) to 37,8 % (B 5) — but in the parenchymatous cases the frequency-figures, on the whole, are not changed.

In order to amplify the results given in the table, a survey has been made of the titres in question during a still later period (C), running from the one-year point and up to about four years after the onset of the pleurisy, and then not only the remaining cases of the Table but also 206 (for AS<sub>t</sub>a 176) other cases, not investigated during period A, have been considered

in addition. The distribution of the cases is now not quite the same as in the table; to one group cases are referred with pulmonary tuberculous processes absent or only very insignificant (in the same way as in Table 1), but initially "pure" cases with later manifestation of tuberculous processes are now included in the other main group, together with the cases with evident pulmonary affections at the time of the acute pleurisy. Progressive cases are otherwise not differentiated from the rest of the material, and consequently the parenchymatous group of period C comprizes serious cases as well as a number of fairly healthy subjects.

Thus a material of 212 AST cases, still pure or almost pure, and 264 with pulmonary lesions, is obtained, and the ASta was also investigated during the same period in 159, and 140, respectively, of the cases. *The frequency figures of the pure cases are now  $21,7\% \pm 2,8$  for the AST and  $32,8\% \pm 3,7$  for the ASta, and among the pulmonary-tuberculosis cases  $29,2\% \pm 2,8$  and  $50,0\% \pm 4,2$ , respectively.* (For the total material of period C the frequency figures are for the AST (476 cases)  $25,9\% \pm 2,0$  and for the ASta (299 cases)  $40,8\% \pm 2,8$ .)

Among the *parenchymatous* cases the figures are both for the AST and for the ASta about the same as these of the first year (columns 11 and 12 of Table 1) — and they coincide equally well with the general incidence in pulmonary tuberculosis cases *without* a preceding pleurisy. Stavenow, (16,) in a material of 1,471 AST cases (190 with ASta), found an AST frequency of 30,0 % and for the ASta 45,9 %.

If the *pure* cases are considered the frequency figures just mentioned ( $21,7\%$  and  $32,8\%$ , respectively) are, on the contrary, particularly reduced as against all the different periods of the first year (cp. columns 1 and 2) — but nevertheless they must be regarded as fairly high. (In "healthy" subjects of the Northern countries a frequency of about 10 % has been found for an elevated AST, and concerning the ASta a corresponding figure of about 15 % might be mentioned.) The great majority of these cases are practically healthy or almost healthy subjects.

An analysis of the figures of Table 1 yields a statistically significant difference (3 times the standard error of the difference)

	Parench. proc:s 0 to +		Parench. proc:s ++		All cases		
	AST >200	Asta >1,0	AST >200	Asta >1,0	AST >200	Asta >1,0	
Exudate	small	38,5 %	55,7 %	21,6 %	62,5 %	33,2 %	57,4 %
	large	52,5 %	56,6 %	47,2 %	61,1 %	51,5 %	57,7 %
Fever	low	37,6 %	54,8 %	20,8 %	63,3 %	33,4 %	56,6 %
	high	59,4 %	59,3 %	43,2 %	60,5 %	54,1 %	59,7 %
S.R.	low	38,3 %	52,3 %	21,9 %	65,6 %	34,2 %	55,4 %
	high	52,0 %	59,4 %	37,0 %	60,6 %	47,5 %	59,6 %
small exudate low fever low S.R.		32,8 %	50,0 %	25,0 %	70,0 %	30,8 %	55,1 %
large exudate high fever high S.R.		63,0 %	60,0 %	67,4 %	63,2 %	64,2 %	60,9 %

Table 2. Frequency of elevated AST and ASa in relation to some clinical data.

for a 6—A 6, A 1—B 1, A 1—C 1, a 1—C 1, A 13—C 13, A 2—C 2, B 2—C 2, A 14—C 14, as well as for A 5—A 11, A 1—A 7, C 2—C 12, and for a 1—a 3, A 1—A 3, B 1—B 3, A 3—A 9, A 15—A 17, and a probable, or very probable difference (2 or 2½ times the standard error) for a 5—A 5, a 13—A 13, a 2—A 2, a 14—A 14, a 16—A 16, B 1—C 1, A 5—B 5, A 9—B 9, A 13—B 13, A 17—B 17, B 14—C 14, as well as for a 5—a 11, a 1—a 7, C 1—C 11, and for A 7—A 9, a 3—a 9, B 3—B 9, a 15—a 17, B 15—B 17, A 2—A 4.

#### *AST and ASa with reference to some clinical symptoms.*

In Table 2 the results are summarized of a comparative investigation (of 527 AST-cases, with ASa in 337) concerning the titre values in relation to (i) the intensity of the pleural process, gauged by the amount of effusion (or tendency to very early relapse), (ii) the temperature during the first month or so, and (iii) the maximum S.R. rate during this period. According to each of the above specifications, the material was divided into two groups approximately equal in size.

Concerning the amount of fluid it will be seen in the table that the cases with a small effusion, which was soon absorbed, on an average carry lower frequency of elevated AST rate than the cases with an extensive or soon relapsing pleurisy (33,2 % as against 51,5 %), and the AST shows practically the

same tendency when the cases with very high or persistent fever, respectively high S. R. (over 50 mm), are compared with the remaining (33,4 % and 34,2 %, respectively, as against 54,1 % and 47,5 %, respectively). To continue with the AST, it will also be noted that (contrary to the data given in Table 1), the differences are not smaller in the "parenchymatous" cases than in the "pure" ones.

The two bottom lines of Table 2 refer to the cases positive from all the three points of view mentioned (127 with AST, 78 with AS<sub>1</sub>a) and the cases "negative" in all three respects (119 with AST, 69 with AS<sub>1</sub>a). *Now the AST-differences are, apparently at least, much more pronounced; 30,8 % as against 64,2 % (in the "pure" group 32,8 % as against 63,0 %, and still greater among the parenchymal cases; 25,0 % as against 67,4 %).*

If then the AS<sub>1</sub>a rates are considered rather different conditions will be noted. The figures for the entire material are fairly uniform throughout. Among the pure cases some very slight difference might be traced (chiefly as regards the S. R.), but the parenchymal cases exhibit an equally slight tendency towards a reverse relation (lower frequency figures in the "positive" cases) and even here the difference is chiefly demonstrated by the S. R. grouping. In the selected groups comprising cases "positive" and "negative" respectively in all the three respects, the AS<sub>1</sub>a shows a reasonably positive relation among the non-parenchymatous cases, but the cases with frank pulmonary processes show a negative relation, statistically still more dubious, however.

If the results of the survey, given in Table 2, are provisionary discussed it may be stated that *the AST is related to the violence of the pleurisy*. This is most clearly apparent in the selected final groups, and it seems worth emphasizing that, as it appears, contrary to the results demonstrated in Table 1, a somewhat larger difference (and the highest frequency-figure) is found among the *parenchymatous* cases. — When attempting to interpret this part of the evidence, it may be said either: if a patient with pulmonary tuberculosis is attacked by a violent acute pleurisy, his liability to exhibit an elevated AST is — on an average — not less than that of the "pure-pleurisy"

cases; or, perhaps rather: that subjects with a high AST are more disposed towards displaying vehement local and systemic responses in acute pleurisy than are the other cases.

As regards the ASta, on the other hand, a characteristic divergence between pure pleurisy cases and parenchymatous cases appears, and a tendency towards reversed relations within the last-named group seems to be worth mentioning. (Cp. the similar behaviour of the ASta in Table 1, column 12, and also the rather high figure in cell a 4). — These observations may be explained by assuming a high incidence of previous staphylococcal influence among the relatively firm tuberculosis cases.

### *Non-tuberculous pleurisy.*

During the past four years 18 cases of acute pleurisy have been observed, in which a tuberculous etiology can be ruled out or appears particularly improbable. — These cases, which are not included among those hitherto discussed, partly derive from the Medical Department.

The AST rates in 5 cases, or 27,7 %, were above the 200-limit, and among 13 cases with ASta titres, there were 7, or 53,8 %, with rates exceeding 1,0. In 7 cases (4 with ASta) of the 18 (13) malignant tumours were to be regarded as the etiological factor. AST frequency 28,5 %, ASta 25,0 %.

Only two cases might be characterized as "rheumatic pleurisy" (the general distinction of this type of disease being of course rather doubtful). Both showed AST rates above 200, one of them a low, and one successively developed a very high ASta.

Cases with a slight pleuritic affection in the course of acute pneumonia or pulmonar embolism are not included in the material just attended to. For a comparison with the unpretentious figures just given (and also with the cases of tuberculous pleurisy) the reader may be referred to a recently published investigation on the bases of a fairly large material of internal-medical cases, (27.) The cases of acute pneumonia showed a frequency-figure of 25,5 % for AST (31,5 % for ASta) and the cases of chronic pulmonary diseases (non-tuberculous) yield the corresponding figures of 16,2 % and 34,1 % (for the

pulmonary-tumour cases 4,5 % and 36,3 %). If the series of pleurisy-cases now discussed is treated in the same way, one case must be excluded, and the frequency figures of 23,5 % for AST, 50,5 % for AS<sub>t</sub>a are obtained (22 % of the patients are above 50 years of age).

It seems reasonable to suppose that the AST in average "non-tuberculous pleurisy" shows a considerably lower incidence of elevation than in the tuberculosis cases. Nearly the same frequency-figures (about 25—20 %) are to be found in cases of acute and chronic non-tuberculous diseases of the lungs. As to the AS<sub>t</sub>a titres, 13 non-tuberculous pleurisy-cases have given a corresponding frequency-figure of about 50 %, as have the tuberculosis cases, but possibly higher than the average of non-tuberculous pulmonary diseases.

### *Discussion.*

Concerning the limits for "normal" titres and the correctness of using one titre-frequency figure only to express the behaviour of a certain serologic reaction within a group of cases, as well as various details of the general interpretation of titres elevated, influence of age, etc., reference is made to a previous paper, (27.) The average age of the patients (in Table 1) is 30 years (3 % above 50 years of age). For the "pure-pleurisy" cases the corresponding figures are 29 years and 2 %, and for the parenchymous cases 32 years and 6 %, respectively. — The problem of individual variations in reacting has also been discussed in the paper just mentioned (p. 563). In the present material the incidence of both titres being elevated and not elevated respectively in the same patient has been investigated in the 299 cases of period C (1—4 years after the acute pleurisy). The probability of both titres being elevated is 13,4 %, but a frequency of 16,4 % is found, and of both titres being low in the same patient, a frequency of 39,8 % is matematically probable, but in 42,8 % of these patients low titres did coincide. (The "pure" cases seem to show the same frequency of coincidence concerning both titres high and low respectively as the pulmonary tuberculosis cases.) These figures might possibly point to some degree of dissimilar individual tendencies, but this factor can hardly be of great importance. — Incidentally it may be repeated now that there is no reason to presume the titre rates obtained being in any way "non-specific". Besides the relation observed in direct bacteriological investigations, etc., a glance at the followed-up cases will indicate that the titre curves as a rule are running quite independently, and also that a rela-

tion to the plasma proteids, as reflected by the S. R., cannot be observed in these graphs.

No doubt the cases of tuberculous pleurisy demonstrate an influence of  $\beta$ -hemolytic streptococci, and also yellow staphylococci, to a very high degree. In fact only proper acute streptococcal diseases (i. e. acute tonsillitis, glomerulonephritis and polyarthritis, scarlatina, etc.) are known to show higher incidence of elevated AST than does the acute pleurisy (and, according to Löfgrens investigations, the Erythema nodosum cases are also to be mentioned in this connection). A higher frequency of the ASTa than in acute pleurisy and pulmonary tuberculosis (apart from the relatively rare cases of certain true staphylococcal diseases) has yet been only demonstrated in chronic polyarthritis, (25, 26.)

On the basis of the facts just mentioned, a discussion of the conception of "rheumatic" pleurisy would be highly tempting, but our actual knowledge ought to be somewhat enlarged before attempting to do so. *Inter alia* it must be emphasized that the bacteria considered in this paper are certainly not the only ones active (besides the tubercle bacillus) in tuberculosis and pleurisy cases (not to enter the field of rheumatic diseases, etc., etc.).

It has been alluded to that, in addition to the studies here mentioned, investigations on the non- $\beta$ -hemolytic streptococci also have been going on in St. Göran's Hospital, and certainly the attempts at finding a clinically applicable serum test even for such streptococci are not given up. Meanwhile an influence of the Escherichias (Coli, etc.) in the tuberculosis cases, apparently somewhat like that of yellow staphylococci, seems to have been demonstrated, (5.) Experiments on animals by Packalén, Bergqvist and others, (6, 7, 12, 13, 14,) about certain details (*inter alia* the "spreading factor" problem) are also being continued, and in this connection it might seem permissible to mention that Dubos, (8,) has recently reported on experiments in co-operation with Horstfall, which were inspired by our research work, and in which a more malignant course of a tuberculous infection was found in animals under the influence of a virus disease.

If thus an approximately comprehensive general discussion on the pathogenesis and practical importance of multiple in-

fections in acute pleurisy still is to be postponed, a few comments on certain present observations may seem justified, however. In the first place it should be pointed out that the activity of  $\beta$ -hemolytic streptococci to a much higher degree than that of the yellow staphylococci seems to be related to acute activity of tuberculous processes, and, to a certain extent, a similar statement might be made with reference to chronic processes and staphylococci.

The fairly great general incidence of an elevated AST now demonstrated in certain practically healthy individuals, and the relatively stable course of a high AST in a rather large proportion of the tuberculosis cases, however, is not quite compatible with a relation of the streptococci to acute processes. A hypothesis of still other detrimental factors — perhaps some other streptococci, or viruses, or a toxic influence of non-bacterial nature — seems reasonable if the development of an acute event on a basis of e. g. streptococci and tubercle bacilli is to be explained (cp. 22).

### *Summary.*

Anti-streptolysin and anti-stapholysin titres in acute tuberculous pleurisy have shown an incidence of AST rates above 200 units in 43,6 % of the entire acute material of 534 cases and, in 340 of these cases, the frequency percentage of the ASta above 1,0 unit was 56,2 %. In the first two weeks somewhat lower percentage figures were obtained (36,6 % and 46,4 %, respectively) and when 3½ months had elapsed, the figures are also lower, (35,8 % and 51,7 %, respectively) than in the main period. — After one year, however, the incidence figure for the "pure-pleurisy" cases are considerably reduced (to 21,7 % for AST and 32,8 % for ASta), but many cases with a favourable course (apparently healthy subjects) may show elevated titres. In the cases with pulmonary lesions the figures (29,2 % and 50,0 %, respectively) are, on an average, not changed after the first year, showing the same frequency as in pulmonary tuberculosis without any pleurisy.

The acute pleurisy cases with a soon progressing tuberculosis on an average show definitely higher frequency figures

(61,9 % and 62,7 %, respectively) than the cases without evident progress (38,5 % and 54,3 % respectively).

Cases without manifest pulmonary lesions exhibit a higher incidence (in 49,1 % and 57,5 %, respectively) of elevated titres than the cases of pulmonary tuberculosis with acute pleurisy (29,8 % and 53,6 %, respectively). In many respects the first-named group shows different conditions as compared with the cases with parenchymal processes.

A statistical analysis has shown significant or probable differences to a satisfactory degree.

On the whole groupings on various principles yield considerably greater differences in the AST than in the AS<sub>t</sub>a. This is especially apparent if the cases with a large pleural effusion, associated with high fever and high S.R., are compared with those showing a small exudate, slight fever and comparatively low S.R.; the AST being elevated in 61.2 % and 30.8 %, respectively, but the frequency of elevated AS<sub>t</sub>a is here almost unchanged.

The behaviour of the titres is presented graphically together with temperature, S.R. and important clinical events in 22 cases, followed up for on an average about two years. Typical rises and decreases are demonstrated, but also cases with the titre rates fairly unmoved (high or low). Some cases were followed up even during a previous Erythema nodosum. In fatal cases a decline of the titres can be observed in the final stage of the disease.

In 18 (13) cases of non-tuberculous pleurisy the incidence of elevated AST was 27,7 % and of the AS<sub>t</sub>a 53.8 %.

Most probably even other bacteria and viruses are of importance in multiple infections, and already this is a reason to postpone a detailed discussion and interpretation. However, the AST is apparently chiefly related to acute processes and the AS<sub>t</sub>a to chronic affections, but a co-operation, or interplay, of still more factors should be presumed to explain a complex etiology.

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## SPLENECTOMY IN THE RETICULOSES

By

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The risks of splenectomy have been greatly reduced in recent years by improvements in surgical and anaesthetic technique, better preoperative and post-operative care, and the introduction of massive transfusion, sulphonamides and penicillin. We have therefore extended the range of indications for splenectomy and have at times advised the operation under circumstances where it could only be a palliative. The present article concerns six such patients who were suffering from diffuse diseases of the blood-forming organs. For convenience, these diseases have been grouped under the heading of *reticulosis*, which is "merely a generic histological term to describe all the progressive hyperplasias of the reticular tissue, including Hodgkin's disease, the majority of the leukaemias and mycosis fungoides, as well as other forms of non-malignant lymphadenopathy" (Robb-Smith, 1944). Nomenclature, histology and prognosis have been reviewed in a recent article by Robb-Smith (1947).

In experimental animals splenectomy causes a moderate anaemia, leucocytosis and thrombocytosis, together with increase in red marrow and compensatory hyperplasia of lymphoid tissue (Perla & Marmorston, 1935). In dogs, for example, the white cell count may rise above 30,000. The interpretation of these changes is complicated by the fact that many animals have latent infections, such as *Bartonella*, which flare up when the spleen is removed. Nevertheless, a prominent leucocytosis rapidly appears in animals in which latent infection may be excluded, and quite apart from operative trauma or infection, removal of the spleen appears to stimulate the mesenchymal

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reticular cells throughout the body to increased function and differentiation. This may be explained by the observations that in the lower vertebrates, and in embryonic life in mammals, the spleen is a blood-forming organ, whilst in post-natal life in mammals it has an important role in the resistance to infection.

In the human subject there is little exact information about the effects of removal of the normal spleen. There is no significant anaemia, but there is a considerable leucocytosis and thrombocytosis. The leucocytosis occurs promptly and may reach high levels. It is not merely a mobilisation of leucocytes but a real increase in production. The proportion of young or non-filament forms of the polymorphs is raised and there is a sustained increase in the lymphocytes. The duration of the rise is difficult to determine owing to the paucity of "normal" human material, but Singer, Miller and Dameshek (1941) give figures which suggest that the white count may remain relatively high for at least three years after splenectomy. A comparable rise occurs in the thrombocytes, though it is probably not of such long duration.

When the spleen is enlarged, as in Banti's syndrome, the white cell and platelet counts are commonly subnormal. Excision of this large spleen is likewise followed by leucocytosis and thrombocytosis, and though the white cells and platelets subsequently fall, they do not again become subnormal.

As was pointed out above, the changes in the white cells and platelets which follow removal of the normal spleen can be regarded as compensatory phenomena. This has been expressed in another way by saying that the spleen exerts an inhibitory influence on the bone-marrow, and when this inhibition is removed, the emission of white cells and platelets from the bone-marrow is accelerated. When the spleen is enlarged, it is possible that it may be responsible for an increased sequestration or destruction of leucocytes and platelets. In such circumstances, splenectomy will not merely remove an inhibition but also prevent destruction. When there is diffuse disease of the blood-forming organs, the conditions are more complicated again and the response to splenectomy cannot be predicted *a priori*. The following six patients are therefore presented as

a factual contribution to a subject on which we have as yet few data.

### *Case Reports.*

*Case 1. Sarcoid spleen removed for pressure symptoms with lasting improvement.*

No. 17190/41. Female, age 36. This woman had a lymph gland removed from the neck at age 31, which was subsequently proved to be an example of Boeck's sarcoid. Five years later she complained of swelling of the abdomen and severe attacks of abdominal pain, which appeared to be the consequence of a considerable enlargement of the spleen. There was a moderate hypochromic anaemia and leucopenia, and the sternal marrow was normal. Splenectomy was advised and a spleen weighing 1780 G. was removed on 31 March, 1942. Dr. A. H. T. Robb-Smith reported, "Sections of the spleen show the typical histological appearances of sarcoidosis, large numbers of small epithelioid cellular collections without caseation which are surrounded by dense fibrous tissue. Intervening splenic tissue show little abnormality, although there are occasional areas of interstitial haemorrhage and a small amount of free iron. Sections of the hilar lymph nodes show a comparable appearance."

When last seen on 17 March, 1947, she was relatively well. She had erythematous skin lesions of Boeck's sarcoid on the arms but no other manifestation of that disease. She had put on much weight and had a more marked hypochromic anaemia, haemoglobin 7.7 G. per cent., red blood cells 5,210,000 per c.mm. Platelets, which had been 250,000 were now 580,000 per c.mm. The white cells before operation had totalled 3,400 per c.mm., with 408 band forms, 1,700 segmented neutrophils, 68 eosinophils, 646 lymphocytes, 578 monocytes. Five years after operation they were 15,200, with 1,520 band forms, 3,800 segmented neutrophils, 304 eosinophils, 304 basophils, 8,056 lymphocytes and 1,216 monocytes.

*Case 2. Sarcoid spleen removed on account of abdominal discomfort. Death from intercurrent infection 1 year later.*

No. 23862/44. Female, age 30. This woman had been ill for four years with iritis, skin lesions and enlarged spleen. She had a moderate normocytic anaemia and severe leucopenia: — red cells 3,770,000 per c.mm., haemoglobin 10.7 G. per cent., platelets 120,000, white cells 1,300 per c.mm., of which there were 130 band forms, 416 segmented neutrophils, 26 basophils, 624 lymphocytes and 104 monocytes. The sternal marrow was normal. Splenectomy was advised because of the abdominal discomfort and a spleen which weighed 2.6 Kg. was removed on 21 March, 1944.

Dr. A. H. T. Robb-Smith reported, "Naked eye, the splenic pulp

is largely replaced by very large numbers of discrete circumscribed 'tubercles' somewhat larger than Malpighian bodies and with a tendency to be arranged in groups; on microscopic examination, splenic tissue and a hilar lymph node have a similar appearance in that the medullary tissue is largely replaced by epithelioid congeries surrounded by a cuff of lymphocytes and with some fibrosis. There is no tendency to caseation or coalescence of the tubercles and giant cells are relatively infrequent. The appearances are typical of *sarcoidosis*."

*Table 1. Case 2.*

Effect of splenectomy on white cells and platelets.

Date	W. B. C.	Platelets
10.3.44 .....	1,300	120,000
21.3.44 .....	<i>Splenectomy</i>	
23.3.44 .....	58,000	415,000
31.3.44 .....	19,350	1,615,000
28.4.44 .....	7,500	1,160,000
25.10.44 .....	9,800	—

A remarkable leucocytosis and thrombocytosis followed the operation; unfortunately no differential white counts were made. The patient was very well for a time, though the number of skin lesions increased. Quite unexpectedly, she had an acute attack of gastro-enteritis and died of cardiac failure on 29, April, 1945.

*Case 3. Lymphoid follicular reticulosis (follicular lymphoblastoma). Large spleen removed on account of leucopenia as preliminary to roentgen therapy. Remission of symptoms but death from haematemesis a year later.*

No. 27271/42. Female, age 50. This woman had had lack of energy, loss of weight and swellings in the groin and armpits for 2½ years. Biopsy of a lymph gland 2 years ago had shown lymphoid follicular reticulosis. She had remained relatively well, without special treatment, till a month before admission when she complained of the discomfort caused by the enlargement of her spleen. She was not anaemic but there were leucopenia and thrombocytopenia (116,000 platelets per c.mm.). Material for sternal puncture was obtained with difficulty but the marrow slides were moderately cellular, with a preponderance of lymphocytes. There was, in fact, a considerable disparity between the blood picture and the marrow.

Splenectomy was advised both for the relief of the abdominal swelling and for the leucopenia, and on 19 November, 1942, a spleen was removed which weighed 1,550 G. Dr. A. H. T. Robb-Smith reported, "Sections of the spleen showed a typical appearance."

Table II. Case 3.

Differential count of blood and bone-marrow before splenectomy.

Case	Blood	Marrow
Neutrophils	Per cent	Per cent
Myelocytes .....	—	3.5
young form .....	—	1.0
Band form .....	3.0	3.0
Segmented .....	60.0	0.5
Eosinophils		
Myelocytes .....	—	0.5
Segmented .....	1.0	—
Basophil .....	1.0	0.5
Lymphocytes .....	27.0	79.5
Monocytes .....	7.0	—
Normoblasts		
Basophilic .....	—	3.0
Polychromatic .....	—	6.0
Orthochromatic .....	—	2.0

rance of lymphoid follicular reticulosis and it is possible to distinguish between the follicles formed of lymphoblasts with a peripheral zone of small lymphocytes and the ordinary Malpighian bodies. Nevertheless, a certain number of these follicles do show macrophages in their centres, which is an unusual feature as far as lymphoid follicular reticulosis in lymph nodes is concerned. The medullary portion of the spleen shows no gross abnormality but an interesting feature is that quite a number of the branches of the splenic vein show sub-intimal lymphoid follicles in their lumen. The hilar lymph nodes show the characteristic appearances of lymphoid follicular reticulosis."

Operation was followed by a moderate thrombocytosis and leucocytosis. Platelets were stabilised at about 450,000 and the white cells between 7,000 and 8,000 per c.mm., with a normal propor-

Table III. Case 3.

Effect of splenectomy on white count.

Date	W. B. C.	Neutrophils
10.11.42 .....	3,000	1,890
19.11.42 .....	<i>Splenectomy</i>	
21.11.42 .....	13,200	—
25.11.42 .....	12,200	8,784
5.12.42 .....	8,800	—
22. 3.43 .....	7,200	3,816
	<i>Radiotherapy</i>	
3. 5.43 .....	1,600	960

tion of neutrophils. A successful course of X-ray therapy by trunk baths was given during March and April, 1943. This patient had a severe haematemesis and died on 2 December, 1943.

*Case 4. Lympho-reticular medullary reticulosis. Splenectomy for leucopenia prior to treatment with nitrogen mustard. Great symptomatic improvement, but Pel-Ebstein fever persists.*

No. 61283/46. Female, age 28. Seven years ago she had swelling of lymph glands in the neck and biopsy revealed an uncommon form of reticulosis — lymphoreticular, which has a relatively good prognosis. She was treated with X-rays and remained well till a year ago, when she was found to have anaemia, splenomegaly, enlargement of abdominal lymph glands and the Pel-Ebstein syndrome. She was treated with transfusions but her condition deteriorated. X-radiation or chemotherapy was contra-indicated by a persistent leucopenia, the total white count ranging between 2,000 and 4,500 per c.mm. The platelets were at a low normal level. On the other hand, she had a very cellular bone-marrow with great activity of the white cell precursors. In March, 1947, therefore, the spleen, which weighed 870 G., was removed. Dr. A. H. T. Robb-Smith reported as follows: "The section shows that the normal architecture of the spleen has been maintained except for focal areas of lympho-reticular proliferation in which there are small congeries of isolated reticulum cells with a lymphoid stroma. There is some degree of fibrosis around these nodules but no increase of reticulin or collagen within the nodules themselves, nor is there any eosinophilic proliferation. There is some degree of diffuse fibrosis of the spleen and a fair amount of iron deposition, but apart from this the general pattern is nor-

*Table IV. Case 4.*  
Effect of splenectomy and nitrogen mustard on white cells and platelets.

Date	Total W. B. C.	Neutrophils	Platelets
13.3.47	2,100	1,386	155,000
20.3.47	4,500	2,655	341,000
25.3.47		<i>Splenectomy</i>	
	26,800	24,656	292,000
27.3.47	10,800	7,884	387,000
8.4.47	13,900	11,815	495,000
15.4.47	12,200	8,662	966,000
		<i>Nitrogen Mustard</i>	
5.6.47	6,600	3,168	438,000
7.6.47		<i>Nitrogen Mustard</i>	
25.7.47	6,700	4,221	277,000
		<i>Nitrogen Mustard</i>	
15.9.47	6,800	4,896	191,000

mal. The circumscribed areas are arranged irregularly in the pulp, not related to follicles or the sinuses. The appearances are identical with those seen in the original lymph node biopsy and must be regarded as a lympho-reticular medullary reticulosis."

Operation was followed by a considerable leucocytosis and thrombocytosis. As soon as the wound had healed treatment with nitrogen mustard was started and three courses were given in the following six months. A remarkable improvement occurred, the weight increased from 53 to 67 Kg., and the catamenia, which had been absent, returned. The Pel-Ebstein syndrome persisted but the height of the fever was diminished. The abdominal glands became impalpable. The haemoglobin remained about 10 G. per cent without further treatment and the white cells were stabilised between 6,000 and 7,000 per c.mm. with a normal differential count. The bonemarrow showed no very striking change.

*Table V. Case 4.*  
Serial sternal punctures.

Case 4	12/2-47	Splenectomy 25/3-47	8/4-47	Nitrogen Mustard 16/4-47	18/4-47	6/6-47
Cellularity .....	+++		++		+++	++
Myeloblast .....	1.4		2.5		1.8	1.0
Promyelocyte .....	19.2		10.0		5.0	5.5
Neutrophil						
Myelocyte .....	15.6		18.5		15.5	27.5
Young form .....	12.2		12.0		11.0	12.5
Band form .....	12.0		12.0		12.0	14.5
Segmented .....	3.6		12.0		16.2	5.5
Eosinophil						
Myelocyte .....	2.8		1.0		2.0	1.5
Segmented .....	2.4		0.5		0.5	0.5
Basophil .....	0.2		—		—	—
Lymphocyte .....	8.2		17.0		18.0	15.0
Monocyte .....	0.6		3.5		2.5	—
Plasma cells .....	—		0.5		0.8	—
Ferrata .....	—		—		—	1.0
Megakaryocyte ....	—		—		0.2	—
Megaloblasts .....	—		—		2.2	—
Pronormoblasts ...	0.6		1.0		0.2	0.5
Normoblasts .....	20.2		9.5		12.0	14.5

*Case 5. Aleukaemic lymphatic leukaemia with haemorrhagic tendency treated by splenectomy and urethane. Long-standing remission.*

No. 51517/45. Male, age 42. This man presented with a history of breathlessness on exertion for four months. He proved to have

small palpable glands in the left side of the neck, an enlarged spleen and occult blood in the stools. The blood count was, red cells 1,340,000 per c.mm.; haemoglobin 4.1 G. per cent, platelets 28,000, white cells 3,100 per c.mm., of which there were 847 neutrophils, 31 eosinophils, 2,087 lymphocytes and 155 monocytes. The marrow was low in cellularity and contained a relative excess of lymphocytes. A cervical lymph node biopsy was performed and was regarded as showing changes suggestive of lymphoid follicular reticulosis and as a result of this report, splenectomy was performed.

However, re-examination of the lymph node showed that the enlarged follicles were of the Fleming's centre type such as is commonly seen in cervical lymph nodes and the main abnormality was a marked proliferation of lymphoid cells in the medulla of the node with an occasional reticulum cell, the appearances essentially those of lymphoid leukosis.

The spleen weighed 890 G., measuring  $24 \times 14 \times 7$  cm. and the cut surface showed no gross abnormality. Microscopic examination showed that the main architecture had been preserved and Malpighian bodies were of normal type, but there was a marked increase of lymphoid cells in the medulla, the appearances again suggesting lymphoid leukosis, but an unusual feature was the marked congestion of the medulla with prominence of the sinuoids and numerous reticulum cells and histiocytes showing erythrophagocytosis. It may be that these unusual appearances are due to the fact that it was a surgical specimen removed shortly after blood transfusion, whereas the examination of the majority of spleens in lymphoid leukosis is only possible after death.

Platelets rose to low normal levels after operation and bleeding ceased. The neutrophils rose to low normal values but there was

Table VI. Case 5.  
Post-operative course of white cells.

Date	W. B. C.	Neutrophils
21. 1.46. ....	4,500	900
22. 1.46. ....	<i>Splenectomy</i>	
23. 1.46. ....		
28. 1.46. ....	5,600	2,800
4. 2.46. ....	5,600	1,867
11. 2.46. ....	11,700	3,259
19. 4.46. ....	17,000	1,700
	45,700	2,285
	<i>Urethane</i>	
21. 5.46. ....		
11.10.46. ....	9,100	637
5. 5.47. ....	8,100	1,053
22. 9.47. ....	12,400	5,704
	14,200	3,834

Table VII. Case 5.  
Serial sternal punctures.

	Ileal Marrow 20/12-45	22/1-46 splenecto- my	Sternal Marrow 1½ hr. after splenectomy	Low	April 1946 Urethane	Sternal Marrow 12/10/46	22/9-47 Low	
Case 5	Low	—	—	—	—	2.0	3.0	
Cellularity	1.0	—	—	0.5	—	2.0	4.5	
Myeloblast	—	—	—	0.5	—	5.0	6.5	
Promyelocyte	3.0	—	0.5	4.0	7.0	4.8	7.0	
Neutrophils	2.0	—	2.0	—	—	—	—	
Myelocyte	2.0	—	0.5	—	—	0.1	—	
Young form	1.0	—	—	—	—	0.1	—	
Band form	—	—	—	—	—	0.5	—	
Segmented	—	—	—	—	—	0.4	—	
Eosinophils	—	—	0.5	—	—	69.8	59.5	
Myelocyte	—	—	—	—	85.0	3.1	—	
Young form	—	—	—	—	—	0.1	—	
Segmented	75.0	—	1.0	—	—	—	—	
Basophils	—	—	—	—	—	0.1	—	
Lymphocytes	—	—	—	—	—	—	—	
Monocytes	8.0	—	—	—	—	—	—	
Undifferentiated stem cells	—	—	—	—	—	—	—	
Reticulum cells	—	—	—	1.5	—	—	—	
Proerythroblast	1.0	—	—	1.0	2.0	—	—	
Erythroblast	6.0	—	—	0.5	0.5	—	—	
Basophil	1.0	—	—	—	—	—	—	
Polychromatic	—	—	—	—	—	—	—	
Orthochromatic	—	—	—	—	—	—	—	

no post-operative crisis or neutrophil leucocytosis. On the other hand, the lymphocytes in the blood gradually climbed to more than 40,000 per c.mm. In April, 1946, he had a short course of urethane, totalling 52 g., and the total white count dropped to 9,100. Thereafter he remained perfectly well without treatment and when last seen on 22 Sept., 1947, he had no anaemia or abnormal physical signs. the platelets were 590,000 per c.mm., the total white cells were 14,200 per c.mm. of which 9,798 were lymphocytes.

Changes in the marrow were not very striking. They are shown in the Table VII.

*Case 6. Aleukaemic leukaemia. Splenectomy on account of obscure leucopenia and thrombocytopenia. No apparent effect.*

No. 74454/47. Male, age 53. This man felt below par for a year and had had several respiratory infections. The spleen was enlarged below the level of the umbilicus. The blood count was, red cells 2,760,000 per c.mm., haemoglobin 8.8 G. per cent., platelets 33,000, white cells 1,800 per c.mm., of which there were 162 band forms, 288 segmented neutrophils, 108 eosinophils, 1224 lymphocytes and 18 monocytes. Sternal marrow was obtained with difficulty; the smears were acellular and the majority of the cells were lymphocytes occurring in clumps. Similar groups of large lymphocytes were found on splenic puncture. In view of the leucopenia and thrombocytopenia, the spleen, which weighed 1140 G., was removed on 17 July, 1947, and Dr. A.H.T. Robb-Smith reported:

"The Malpighian bodies are inconspicuous and there is a diffuse medullary increase of primitive haemic cells, which show very little differentiation. There are scattered eosinophils and eosinophil myelocytes and also a certain number of basophils, but the majority of cells are small in size, with a clearly primitive type of nucleus, rounded to slightly indented. There are features making it a little suggestive of an atypical monocyte, but I am not really satisfied about this and could not exclude the possibility of this being an example of leucopenic myelosis. All that I would feel confident about is that this is a leukosis, but the cytology is difficult to analyse in spite of the use of haematological stains".

The operation had little immediate effect on the white cells. There was, however, a slow rise in the lymphocytes, which had reached 5,760 by 2 October, 1947. The platelets remained at more normal levels, and the rise in red cells which had been brought about by transfusion was maintained.

#### Discussion.

Certain principles have been followed in the selection of these six cases of reticulosis for splenectomy. We have excluded

*Table VIII. Case 6.*  
Effect of splenectomy on white cells and platelets.

Date	W. B. C.	Neutrophils	Platelets
8. 7.47. ....	1,800	450	33,000
15. 7.47. ....	1,600	352	13,000
17. 7.47. ....	<i>Splenectomy</i>		
18. 7.47. ....	2,000	480	76,000
28. 7.47. ....	2,100	630	115,000
3. 9.47. ....	3,700	407	23,000
2.10.47. ....	7,200	1,368	121,000

patients with a short history; patients with frank leukaemia, because X-radiation is probably more effective in leukaemia when the spleen is intact; and patients with non-leukaemic myeloid splenomegaly (myelosclerosis) because they are known to do badly (Bukh and With, 1945). In addition, we have demanded some positive indication for splenectomy, such as pressure symptoms from the spleen (2 cases), leucopenia (2 cases), thrombocytopenia (1 case) and diagnostic obscurity (1 case). No special operative difficulties were experienced and no ill effects. The late results were excellent except in one case of aleukaemic leukaemia. There was great symptomatic improvement, weight and strength were gained, and anaemia, leucopenia and thrombocytopenia were relieved.

Of our positive indications for splenectomy, the most doubtful is leucopenia. Decker, Leddy and Desjardins (1932) in an analysis of a large group of cases of reticulosis ("lymphoblastoma") found that patients with white blood counts below 5,500 per c.mm. tolerated roentgen treatment quite well. It is clear, therefore, that leucopenia should not be regarded as a contra-indication to treatment by X-rays, radioactive phosphorus, nitrogen mustard or similar agencies, particularly now that attacks of agranulocytic infection can usually be controlled by penicillin. If, however, leucopenia forms a bar to the effective use of these agents, then splenectomy is probably advisable as a form of the "surgery of access".

It is possible that operation is more likely to be successful when the bone-marrow is normal, but we have not regarded an abnormal myelogram as a contraindication. In 2 cases of sarcoidosis and 1 atypical Hodgkin's disease, the marrow was relatively normal and the changes in the blood after splenectomy

were much like those we have seen after splenectomy in Banti's syndrome and kala azar. Leucopenia and thrombocytopenia were replaced by normal or high normal levels of white cells and platelets. The three remaining patients had a relatively acellular and lymphatic type of marrow. One (lymphoid follicular reticulosis) showed a low normal response to splenectomy, the second (aleukaemic lymphatic leukaemia) developed a notable lymphæmia which responded to urethane, the third (aleukaemic leukaemia) has shown a moderate rise in lymphocytes in the short period of observation since splenectomy.

From these data, which have been analysed in retrospect, it is not possible to say to what extent leucopenia and thrombocytopenia in the reticuloses are due to increased cell destruction in the spleen, inhibition of the marrow by the large spleen, and infiltration of the marrow by the abnormal tissue. We did not observe any gross changes in the marrow after operation. Limarzi and co-workers (1943) reported that after splenectomy in Banti's disease there was no change in the cellularity of the marrow but an increase in the myeloid-erythroid ratio and slightly increased maturity of the myeloid elements. Engelbreth-Holm (1938) has made a similar observation after splenectomy in "tuberculous splenomegaly" (? sarcoidosis) and Schousboe (1940) in Hodgkin's disease and Banti's syndrome. Engelbreth-Holm concludes that the spleen controls the maturation of the cells in the marrow and their emission into the blood stream, and this function is exaggerated when the spleen is enlarged. Changes in the bone-marrow, the polymorphonuclear leucocytes and the blood platelets after splenectomy are complicated by the effects of the operative trauma. Changes in the lymphocytes are not likely to have been brought about in this way. In two of our six patients there was a notable increase of lymphocytes after operation, in one revealing a leukaemia. This is certainly suggestive of a splenic control of the number of lymphocytes in the blood.

In conclusion, we wish to emphasise that these six patients represent only a small fraction of those with reticuloses whom we have seen during the same period. Nothing is further from our intention than to advocate indiscriminate operation in the reticuloses. The proportion in whom the symptoms can be even

temporarily relieved by splenectomy will always be small. Nevertheless, our results indicate that there is this small proportion in whom splenectomy may be fully justified, in the same way as palliative operations are justified in other forms of malignant disease. Our results also indicate that when similar patients are submitted to splenectomy in the future, it will be of value to carry our more quantitative studies of the marrow and more detailed cytological examination of the fresh spleen (Doan and Wright, 1946), in the hope of learning more about the morbid physiology of these diseases.

#### *Summary.*

1. Splenectomy has been carried out in 2 cases of sarcoidosis, 1 lymphoid follicular reticulosis, 1 lympho-reticular medullary reticulosis, and 2 aleukaemic leukaemia.
2. The indications were pressure symptoms (2 cases), leucopenia (2 cases), thrombocytopenia (1 case) and diagnosis (1 case). Satisfactory relief of symptoms was achieved in 5 out of the 6 patients.
3. The changes in the blood and the bone-marrow after splenectomy are briefly described.

I am greatly indebted to Mr. D. C. Corry and Mr. A. Elliot-Smith, who operated on the patients, and to Dr. A. H. T. Robb-Smith, who made the pathological reports.

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# ACTA MEDICA SCANDINAVICA

SUPPLEMENTUM CCXIV

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EXAMINATION  
INTO THE DIET OF NORWEGIAN  
FAMILIES DURING THE WAR-YEARS  
1942—45

BY  
*AXEL STRØM*

ACCOMPANIES VOL. CXXXI

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CENTRALTRYKKERIET, OSLO 1948

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From the  
Institute of Hygiene, University of Oslo. Director: Professor Axel Strøm, M. D.

EXAMINATION  
INTO THE DIET OF NORWEGIAN  
FAMILIES DURING THE WAR-YEARS  
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BY  
*AXEL STRØM*

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Acta Medica Scandinavica. Supplementum — —

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## Introduction.

The diet of Norwegian families has been repeatedly investigated during the present century, notwithstanding which we have, even in ordinary times, a very limited knowledge of the diet of the Norwegian people. None of the investigations has been sufficiently representative and comprehensive to give other than fragmentary information. Especially inadequate is our knowledge of the diet of the rural population.

Earlier investigations are of two categories:

(1). Statistical examinations whose principal object has been the ascertainment of the cost of living with a view to index calculations. These examinations have been based on household accounts kept for a fairly long period, up to 1 year.

(2). Investigations by doctors of the dietary of certain population groups. Though these have been considerably more thorough they have, on the other hand, comprised relatively few families and covered shorter periods, from 1 to 4 weeks.

The most important earlier surveys are:

(1). Examination by the Central Bureau of Statistics of the budgets of 12 Oslo labourer families for 1 year from May 1st., 1906.

(2). Examination by the Statistical Office of Christiania municipality, into household accounts of 171 less prosperous families in a number of Norwegian towns, during a period dating from Sept. 1st. 1912 to Aug. 31st. 1913.

(3). Survey by the Central Bureau of Statistics, of the effect of the high cost of living during World war I on the diet. The survey included labourers and functionaries in a number of Norwegian towns. 651 accounts were kept in August 1916 as against 534 in February 1917.

(4). Survey (1918-19) by the Central Bureau of Statistics of the effects of the foodrationing. The survey covered a period of 1 year from Sept. 9th. 1918 and comprised the household accounts of 48 labourers, 20 minor functionaries, and 14 other

functionaries. Of these accounts, 51 were from Oslo and 31 from Bergen.

(5). Examination (1927-28) by the Central Bureau of Statistics. This included 166 complete, yearly accounts of 135 labourers' families (Oslo 44, Bergen 42, Stavanger 12, Trondheim 22 and Drammen 15) and of 31 other families.

(6). *Gerhard Hertzberg's* examination into: Nutrition, health and environment in Dale, Bruvik, Western Norway. The examination included the families of 21 labourers, 7 higher functionaries, 4 minor functionaries and 3 small farmers. It was made during 3 separate weeks: winter, spring and autumn of 1930-31.

(7). *Karl Evang's* and *Otto Gallung Hansen's* investigation (1933) of the diet of 301 poorly situated families. The breadwinners were forest workers, agricultural workers, smallfarmers and industrial workers. The investigation was carried on during 4 weeks of May and June 1933.

(8). The *Karl Evang, Otto Gallung Hansen* and *Johannes Lund* investigation (1935-36) in Bjarkøy, Northern Norway. The investigation included 7 families and was made in 3 periods: 4 weeks in September-October 1935, January-February 1936, and September-October 1936.

(9). Investigation (1936-37) by *Karl Evang, Otto Gallung Hansen* and *Halvard Lid* in Lodingen, Northern Norway. The investigation comprised 22 families and was made in periods of 4 weeks: May-June 1936, September-October 1936, and January-February 1937.

(10). The *Karl Evang* and *Otto Gallung Hansen* investigation (1936-37) in Oslo and its vicinity. The investigation included 181 families, of which 88 were in Oslo. 117 families were investigated in 3 periods, the others in 1 or 2 periods.

The investigations referred to in 8, 9 and 10 have, as yet, been made public only in part.

(11). *Gert M. Høy's* investigation (1937-38) in Valle, Setesdal. It included 15 families, 10 of which lived on the typical, old-fashioned «Valle-diet». The investigation was made during periods of 14 days, in April 1937 and September 1938.

(12). *Ole Storstein's* survey (1938) in Skånland. It comprised 9 Lapland families and proceeded for a period of 4 weeks during November-December 1938.

(13). The *Olto Gallung Hansen* investigations (1941-46). The investigations, not as yet concluded, have, for the most part, comprised Oslo families. They have been carried on in periods of 2 weeks, generally 3 periods per year. The number of families participating in the different series has varied from 73 in the first (February-June 1941) to 31 in the January-February series in 1943. The results have not yet been made public.

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The investigations undertaken by the Institute of Hygiene were occasioned by the fact that during the war, in my capacity as medical inspector at A/S Freia chocolate factory, I remarked a loss of weight among the employees, notwithstanding the generous contribution made them by the company to augment their food supply.

An investigation was therefore undertaken among Freia's employees, and with the assistance of the medical inspector of A/S Electric Bureau, *Haakon Natvig* M. D., a similar one among the employees at this factory. Both concerns manifested great interest in the undertaking and made contributions to its financial support.

It was originally planned to begin similar investigations in a number of other concerns in Oslo and, if possible, over the country, but for various reasons this plan was abandoned. Firstly: it was imperative to keep the investigations secret from the then existing authorities, who, one could safely assume, would misuse the findings if they came into possession of them. This necessity for secrecy complicated the investigations and tended seriously to limit their extent. Secondly: the workers as a rule proved reluctant to participate in the investigations. This was not due to prejudice against this sort of investigation, but to a very reasonable suspicion that the investigations—all assurances to the contrary notwithstanding—were of nazi instigation, and should therefore be met with sabotage. Only in those concerns with which we had previously been connected, such as Freia and Electric Bureau, were we at no such disadvantage, and not even in these concerns was it easy to get a sufficiently large number of families; for one thing, the housewives regarded the accurate keeping of accounts and weighing as too

great a burden to assume, considering all the other work and standing in queues. Then there were many who declined to participate because of unwillingness to put on record what sort of food they had in their larders. (The black market was patronized by all classes). The number of families was further reduced by the fact that some of the questionnaires were so imperfectly filled in as to be useless.

Outside Oslo it was possible to undertake only one survey, at Arendal and Hisøy, where the health officer *Stian W. Erichsen* M. D. assumed the work. This undertaking, however, had to be abandoned after a time as a result of a rumour circulated to the effect that the survey had been instituted by the rationing authorities with a view to reducing rations. It proved impossible to continue the work in the face of such a rumour.

### Material.

At the Electric Bureau a total of 5 surveys were carried out. The first was made in January 1943, the second in June 1943, the third in May 1944, the fourth in November-December 1944 and the fifth in May 1945. In all 17 families participated in these surveys; but only 5 participated in them all; the others were examined from 1 to 4 times. The number of families participating in the various surveys was 14, 10, 7, 7 and 13 respectively. See table 1.

At Freia there were 3 series of investigations. The first was made in November-December 1942, the second in October-November 1943, and the third in May 1944. The reason for not continuing these investigations beyond that date was that from August 1944, the factory began to make the «Svedish Soup» which was served school children, old people, inmates of orphans homes and others. The soup, which was very nourishing, was served to the workers in such large and varying portions that it was considered impossible to ascertain how much their food had been augmented in this way. Altogether, 16 families participated in these investigations. Only 6, however, took part in all 3; the others were examined once or twice. The number of families in the various investigations were: 11, 12 and 8.

Table 1: *Number of man values in the families investigated.*

Fam. no.	Investigation-series:									
	EB I	EB II	EB III	EB IV	EB V	F I	F II	F III	A	H
1	1,90	2,15				3,33	3,43	3,36	3,33	1,43
2	2,63	5,23	5,43		5,53	3,41			4,23	8,79
3	3,49	3,49	3,49	3,49	2,66	2,83			3,83	2,83
4	3,73	3,73	3,73	3,73	3,83	2,33	2,33		4,56	3,03
5	4,66	3,83	3,66	1,83	1,83	1,58	1,58	0,83	4,43	1,50
6	2,73	2,73			2,35	1,83	1,83	1,83	2,63	5,13
7	3,88	3,13	3,52	3,33	2,53	0,83	0,83	0,83	4,03	3,63
8	2,63	2,83				0,83			2,58	4,89
9	2,63	2,43		1,83	1,83	0,83	0,83	0,83	5,85	4,46
10	2,43	2,43	2,53	2,53	2,53	0,83			2,83	
11	2,43		2,53	2,53	3,53	0,83	0,83	0,83	2,66	
12	2,63						1,83	1,83		
13	2,43						1,66			
14	2,93				3,13		0,83	0,83		
15					3,49		0,83			
16					2,83		0,83			
17					2,33					
<hr/>										
Tot.	41,13	31,98	24,98	19,27	38,40	19,46	17,64	11,17	40,96	35,69
									= 280,59	

Orphan homes I: 19,04

—»— II: 15,72.

In Arendal and Hisøy only one series of investigations was made, in November-December 1943. This included 11 families in Arendal and 9 in Hisøy. Two orphans' homes were also investigated, one in Arendal and one in Hisøy.

Table 2 shows the number of persons in the families examined in each separate series. The families were generally small, consisting as a rule of 3 or 4 members. The Freia families were especially small. Of the 16 «families» examined at this factory, 6 consisted of a single person. At Freia, during the war, there were relatively few who supported families; unmarried, elderly women comprised, to a large extent, the labour force of the factory, and this was reflected in the composition of the material.

The number of children under 15 years was small in the Oslo material, particularly in the Freia «families». In the Arendal and Hisøy material the number was somewhat larger. Table 2.

Table 2: *Number of persons in the families investigated.*

No	Investigation series:										Total
	Electric Bureau					Freia			Aren-	Hisoy	
	I	II	III	IV	V	I	II	III	dal		
12	0	0	0	0	0	0	0	0	0	1	1
7	0	0	0	0	0	0	0	0	1	0	1
6	0	1	1	0	1	0	0	0	2	3	8
5	2	1	1	1	0	0	0	0	2	0	7
4	4	3	3	2	5	2	1	1	3	2	26
3	7	5	2	2	5	2	1	0	3	1	28
2	1 <sup>1</sup>	0	0	2	2	2	4	2	0	2	15
1	0	0	0	0	0	5	6	5	0	0	16
Number of families	14	10	7	7	13	11	12	8	11 <sup>2</sup>	9 <sup>3</sup>	102
Number of families with children under 15 yrs. ....	11	7	5	4	8	2	2	1	7	7	
Number of children under 15 yrs. ....	14	10	8	5	11	3	3	2	17	22	

<sup>1</sup> Wife 6 mos. pregnant. <sup>2</sup> Investigated also an Orphan home (Orphan home I) with 5 adults and 19 children under 15 yrs. <sup>3</sup> Investigated also an Orphan home (Orphan home II) with 5 adults and 16 children under 15 yrs.

Table 3 shows the age and sex-distribution of the families examined, in the first survey in which they took part. Also in this table it is apparent how few younger people are represented in the Oslo material.

Table 3: *Age- and sex distribution of the families in the first investigation in which they participated.*

Age in yrs.	E. B.			Freia			Arendal			Hisoy		
	M	W	total	M	W	total	M	W	total	M	W	total
0- 1	0	0	0	0	0	0	1	0	1	0	0	0
1- 4	1	2	3	0	1	1	1	3	4	1	4	5
5- 9	5	3	8	0	1	1	5	2	7	2	4	6
10-14	2	2	4	0	1	1	3	2	5	6	5	11
15-19	3	2	5	1	0	1	6	3	9	1	3	4
20-64	18	20	38	6	17	23	11	12	23	6	9	15
65 a.m.	0	1	1	1	2	3	0	1	1	2	2	4
All ages	29	30	59	8	22	30	27	23	50	18	27	45

## Method.

The examination periods were of 14 days duration. At the beginning of every period, the family was visited by an assistant who got information from the housewife concerning the number of members of the family, their age and occupation, number of meals per day, food habits etc. Together, she and the housewife weighed the food on hand and recorded its sort and quantity. As a rule all food was weighed; the only supplies excepted were those which the housewife declared were not for consumption during the period of investigation (such statements were verified later), and food of which the families had large stores, as potatoes and similar things. In the latter case, the housewife was directed to weigh daily the quantity taken from the store and enter it on the chart for that day.

During the same visit, the assistant explained the method of procedure and gave the housewife a chart for each of the 14 days. On these the housewife was to note daily the kind and quantity of food bought, or acquired in other ways. She should, furthermore, write down the kind and quantity of food taken out of the house or used as animal feed. Ordinary household waste was not to be recorded as it would be taken account of in another way. If any member of the family had eaten any meal away from home and the food was *not* brought from home, exact information as to its content and quantity was to be given. If there were guests for any meal, the housewife was to designate which meal, the number of guests, as well as their age and sex.

On the other hand, the chart took no account of the price of food bought. Usually, in investigations of this kind, it is of great importance to include information regarding the cost as, under normal circumstances, the food of the family depends for a great part on the family's financial status. During the war, however, conditions were not normal; all classes were well off as to money and the dietary was determined by availability in a far greater degree than by financial standing. Information as to the price of food was therefore of less importance under these circumstances than it would otherwise have been. There was also a special reason for not including such a question; a great

majority of families procured larger or smaller quantities of food «illegally» and at prices higher than those fixed by the authorities. This applied to our families in no small degree. They were willing to put this food on the records but it was evident that they were reluctant to put the prices down in black and white. Rather than risk the families' withdrawal from the investigation or getting incorrect information, we decided not to include this sort of question.

To insure that the charts were filled out as accurately and circumstantially as possible, during the first periods our assistant visited the families every few days. Families that had participated during several periods were visited less often, once it was apparent that the visits were not necessary.

At the conclusion of the period, food supplies on hand, were again weighed, and the findings noted.

On the basis of the two weighings and the daily records, the consumption of the various foodstuffs during the period of investigation was calculated. As customary, the calculations were carried out per man value per day.

Of the numerous co-efficient scales in use, we chose *Catheart* and *Murray's*. This scale was chosen owing to the fact that it has been employed in the majority of previous investigations in Norway, as in those made by *Evang*, *Galtung Hansen* and associates, as well as by *Høye* and *Storstein*.

If any members of the family had eaten one or more meals away from home and had not taken the food with him, we tried, as a matter of principle, to ascertain the sort and quantity and added it to the family's consumption for that day.

But when it was impossible to obtain the required information as to the composition of the meal, a correction of the man value of the individual in question for that day was inserted, deducting respectively  $\frac{1}{3}$  of the value for each of the meals: breakfast, dinner and supper. When the families had guests, we proceeded in the same manner, making additions of the same size to the man value of the family for that day.

The calculation of the contents of nutrients of the food as purchased was mainly undertaken on the basis of *E. H. Schiøtz's*: «Kostlære». Schiøtz's table is based chiefly on *Groth-Pedersen's* comprehensive table, but Norwegian investigations receive a

somewhat more prominent place. Besides Schiotz's table, we made use of Groth-Petersen's table, and in a few instances, of *Schall's* «Nahrungsmitteltabelle».

The calculation was, however, complicated by the fact that during the war the composition of a number of foodstuffs was quite different from that of ordinary times, and consequently there was no information about them in the tables. We were therefore obliged to procure our own figures for a number of foodstuffs. The chemical division of the Oslo Departement of Health gave us analyses of such foods as cod, salted and steeped in lye, kippers and «Klippfisk». Information as to bread and bakery products we received from Dr. chem. A. *Schulerud* of Kristiania Breadfactory; and the various producers informed us of the composition of the different spreads they made for use in sandwiches. Margarine factories gave us informations as to the amount of butter and vitamins contained in margarine. The content of nutrients of a few prepared foods, such as fish-pudding, fishcakes and things similar, had to be calculated from the recipes current at that time.

In computing the caloric value of the food we used the *Atwater's* figures: 4, 9, 4 calories per gram of protein, fat and carbohydrates respectively. These figures allow for loss in absorption, but not for loss due to waste. According to *Bigwood*, the amount of household waste in European families varies considerably: from 1½ % in poor families to a considerably higher per cent in more prosperous classes. We decided that 2 % was a reasonable deduction for our families as there was undoubtedly a minimum of household waste during the war. For the orphans' homes we made a deduction of 10 % as experience has shown that there is appreciably greater waste in institutions than in homes, and particularly great in orphan asylums.

## The Composition of Diet.

Table 4 shows the average intake of the individual foodstuffs per man value per day. The table gives the figures for each investigations series, and the average values for the Oslo series, for those of Arendal-Hisoy, and for all the investigations.

Table 4: Average consumption of the various foodstuffs per man value per day.

Table 4: Average consumption of the various foodstuffs															
	Electric Bureau					Freia			Arendal Hisøy		Oslo	a. Hisøy	Arendal	Total homes	
	I	II	III	IV	V	I	II	III	*	*					
Foodstuffs															
Meat and meatprod.	30,87	22,08	16,63	43,90	64,75	38,33	16,46	13,77	29,07	38,15	32,29	33,65	32,56	12,45	
Fish and fishproducts	317,90	384,77	408,07	212,85	211,75	231,34	246,64	343,51	268,29	235,22	292,08	253,40	284,50	79,42	
Wholemilk .....	314,86	247,76	193,37	256,20	231,48	239,76	277,79	163,19	288,59	287,82	247,78	288,25	255,72	574,49	
Sk. milk .....	137,20	167,81	91,29	16,89	67,11	202,38	177,05	184,45	125,01	95,24	134,82	111,61	130,27	81,17	
Condensed a. o. milk	8,70	10,04	45,86	4,75	20,20	23,79	28,73	4,50	15,98	4,72	19,50	10,92	17,81	5,16	
Butter .....	21,14	28,18	28,83	16,03	20,28	25,79	22,32	21,51	36,01	27,99	22,47	32,41	24,42	32,14	
Margarine a. o. fats..	21,15	23,49	14,68	3,24	1,46	5,65	1,09	2,05	2,21	4,52	4,23	3,25	4,04	8,60	
Cod-liver-oil .....	9,27	4,94	4,95	3,18	2,96	11,44	4,21	7,66	6,31	0,94	2,73	3,89	2,96	0,52	
Cheese .....	14,56	34,08	18,68	3,44	6,35	0,48	2,71	7,66	342,95	326,59	322,27	335,58	324,88	208,86	
Egg .....	0,28	0,41	3,44	1,47	351,28	213,06	259,35	306,28	96,51	87,69	105,58	92,54	103,03	237,66	
Bread and pastry ...	373,75	387,39	363,09	343,49	90,15	120,34	93,40	110,14	83,51						
Bread and meal.....	112,54	83,06	148,46												
Flour and flour com-				354,38	390,56	257,30	309,63	319,11	360,32	338,90	355,35	350,68	354,43	391,68	
Bread as flour .....	400,03	381,05	438,37	503,96	481,39	553,38	524,55	538,91	763,73	672,29	557,81	722,59	590,12	757,42	
Potatoes .....	650,65	621,18	562,91	210,80	95,78	319,88	300,05	63,48	299,42	251,41	169,48	277,81	190,72	509,86	
Fresh vegetables ...	178,91	82,89	30,85	7,94	10,23	5,96	1,03	2,08	2,41	6,20	6,03	4,12	5,66	0	
Dried vegetables ...	9,84	7,41	0												
Fruit, berries, jam &	42,43	29,57	23,60	51,38	21,55	56,32	183,26	74,62	71,77	147,84	62,33	106,05	70,90	116,51	
juice .....															
Sugar, syrup & sugar															
spreads .....	38,97	37,00	33,86	31,86	35,35	30,59	43,26	29,10	30,69	25,41	35,65	28,31	34,21	41,26	
Sundries (chocolate,															
cocoa, ale) .....	1,05	57,44	0	0	0,20	24,20	32,21	0,21	1,76	0	15,20	0,97	12,32	1,30	
* Orphan homes not included.															

\* Orphan homes not included.

Table 5: Food consumption in different diet-investigations in Oslo.

	Christiania Statistical office	Central Bureau of Statistics	Central Bureau of Statistics	Central Bureau of Statistics	Evang and Gallung- Hansen	Strom	Plan of State Food Council
	1912-13	1916-17	1918-19	1927-28	1936-37*	1942-45	1939
Meat + meat products ..	99.2	75.4	122.0	152.4	157.5	32.3	83
Fish + fish products ...	68.3	97.6	92.3	90.5	98.7	292.1	152
Wholemilk .....	236.8	339.8	342.9	433.6	544.4	247.8	728
Skimmed milk .....	283.7	539.2	524.5	427.1	558.3	621.7	402.1
Condensed a. o. milk ..	18.7	33.3	16.2	32.2	18.0	134.8	429
Cream .....	30.3	20.6	27.5	17.2	22.7	19.5	
Butter .....	20.9	9.1	9.6	9.7	21.1	0	
Margarine a. o. fats ....	41.3	53.4	16.0	67.1	60.4	21.7	26
Cod-liver-oil .....						24.4	43
Cheese .....	20.4	17.8	15.9	26.1	30.0	4.0	11
Egg .....	13.2	6.0	13.7	31.5	39.2	11.9	34
Bread + pastry .....	299.6	338.1	327.3	291.5	288.4	2.0	28
Flour + meal .....	131.2	110.7	114.1	67.9	62.1	322.3	269
Potatoes .....	217.7	213.4	359.4	270.8	268.6	105.6	63
Fresh vegetables .....	21.3			49.6	88.0	557.8	533
Dried vegetables .....	4.4		1.3	7.2	8.9	169.5	142
Fresh fruit + berries ..	38.4		12.3	63.2	124.4	6.0**	6
Other fruit .....	4.1	43.8		11.9	73.1		
Juice + jam .....	1.3		2.6	8.2	6.3	62.3	117
Sugar .....	55.9	61.2	60.2	1.7	28.1		
Syrup .....	5.3	67.8	71.2	69.5	62.5	35.7	13
Coffee .....	13.2	3.4	7.5	67.7	74.8	71.2	
		15.6	12.8	5.3	8.7		
				16.2	16.8	0	9

\* For self-supporting families. \*\* Includes peas, beans + lentils.

In table 5 our results from Oslo are compared with the results of some of the investigations previously carried out among workers in Oslo. Likewise in table 6 the average values for all our investigations are compared with results of a number of other dietary surveys made during the past 15 years.

In judging these tables one must, however, be aware that the figures are not in the strictest sense, comparable. Different methods have, in part, been employed in the investigations, and the figures have not always the same meaning. For instance, the official, statistical investigations give inadequate information regarding consumption of vegetables. The investigations of 1912-13 and 1918-19 have information on the consumption of cabbage only, while those made in 1927-28 give figures as to the consumption of cabbage and carrots. The figures for the official, statistical investigations of the consumption of butchers' meat, also comprise wares of little nutritive value, such as soup-bones etc. In the other investigations, our own as well, such wares are not included in the figures for meat. In some investigations the calculations have been based on the American man-value scale, while in others Cathcart's has been used. This is of less importance in the relatively rough comparison between intake of the various groups of foodstuffs. The difference between the families' financial status, the food to which they are accustomed, etc. is, however, of greater importance. All the investigations comprise relatively few families, and it is therefore impossible to disregard the effect of such factors.

In order to judge the diet during the war, it is imperative to bear in mind how peoples' dietary, especially in cities, changed during the 20 or 30 years before the war. This change, clearly shown in table 5, is first and foremost characterized by increased consumption of protective foods. From 1912 to 1939 there was greatly increased consumption of meat, fish and whole milk in Oslo, while consumption of skimmed milk decreased. The total consumption of butter and margarine, eggs and cheese rose considerably. There was undoubtedly increased consumption of fresh vegetables, fruit and berries, though information regarding these foodstuffs is incomplete. In the other hand, the use of cereals—bread, pastry, flour and porridge—went down, while the consumption of potatoes fluctuated. Besides

Table 6. *Consumption of food in some Norwegian Dietary investigations.*

	Hertzberg		Evang and Galtung-Hansen		Evang a. o.		Evang a. o.		Hoye		Storstein		Strom - All investi- gations
	Date	1933	Galtung-Hansen	Lodingen	Bjarkoy	Valle	Skånland						
Meat + mealproducts ..	107	46,1		48,2	58,0	52	69,2						32,6
Fish + fishproducts ...	129	41,8		280,9	236,7	5 (netto)	262,4						284,5
Whole milk .....	724	314,0		508,1	469,0	343	562,8						255,7
Skimmed milk .....		211,0		34,1	11,6	1335	0						130,3
Condensed a. o. milk ..		0,9		0,3	0	0	0						17,8
Cream .....	17	2,7		0,2	6,7	36	0						0
Butter .....	23	3,9		1,4	6,6	55	0,9						19,6
Margarine + other fats .	45	50,2		61,2	66,1	5	64,5						24,4
Cod-liver-oil .....	0	0		0	0	0	0						4,0
Cheese .....	16	15,3		8,2	10,6	19	18,3						10,0
Egg .....	17	14,0		4,0	12,2	1	0						2,3
Bread + pastry .....	342	69,6		48,4	29,3	202	256,5						324,9
Flour + meal .....	67	313,1		419,5	350,3	224	299,8						103,0
Flour, meal, bread etc. computed as flour ....	330	366,6		456,7	372,8	379	497,1						354,4
Potatoes .....	257	390,6		401,4	355,3	466 (netto)	796,2						590,1
Fresh vegetables .....	57	9,8		14,5	51,9	11	25,6						190,7
Dried vegetables .....	6	2,9		3,8	1,2	5	0						5,7*
Fresh fruit + berries ..	56	0,8		8,8	46,7	14	0,6						
Other fruit + berries ..	31	0,8	2,5	3,2	6,0	0	2,5	20,9					70,9
Juice + jam .....		0,9		26,2	23,8	15	17,8						
Sugar .....	50	51,1	51,8	56,7	55,2	33	43,5						34,2
Syrup .....	20	0,7		22,0	32,2	0	20,2						63,7
Coffee .....	12	10,8		12,0	16,2	6	10,6						0

\* Includes peas, beans and lentils.

these changes there were also others which are characteristic of a higher standard of living: increased consumption of sugar and coffee.

Compared with this, the chief feature of the diet of the wartime was a decrease in the consumption of meat, fat, whole milk, cream, cheese, eggs, margarine (but not butter), berries, fruit, sugar and coffee. Consumption of skimmed milk increased, though not sufficiently to compensate for the decrease in consumption of whole milk. Thus the total consumption of milk was less than it had been before the war. There was a somewhat greater consumption of cereals and a much greater consumption of potatoes, fresh vegetables and fish. While all of these changes cannot be characterized as unfavourable, it can, already after this analysis, be given as a general characteristic of the war-time diet that, from the standpoint of nutrition, it was unquestionably inferior to the prewar diet.

In the last column of table 5 are entered the quantity of individual foodstuffs which our families should have had according to the suggestions of the State Food Council of 1939. This Council was appointed by the government in the autumn of 1939 to decide the state's food policy during the war. Early in 1940 it presented a proposal for a national dietary in the event of the country being partially cut off. The german invasion of Norway nullified the work of this Council and, as the tables show, the diet on which we lived during the war diverged widely from that proposed by the Council. The consumption of meat, milk, butter, margarine and other fat, cheese, eggs, fruit, berries, sugar and coffee was lower than the Council planned it should be, while the consumption of fish, cereals, potatoes and vegetables was higher.

The consumption of individual foodstuffs was as follows:

The average daily consumption of *butcher's meat* was 32,3 grs. per man value. This is the lowest value ever found by any earlier investigation in this country. Even the families on relief, which were examined by *Evang* and *Galtung Hansen* in 1933, had a higher consumption average. In judging the figures it is necessary to take into consideration the fact that several of the families received the extra meat ration allotted for heavy labour; without that the figures would have been still lower. 13 families, or

12,8 % of the total, consumed no meat during the period of investigation (table 7).

Table 7: *Consumption of meat and meat products in the various families.*

Grams per M. V. per day	0	1-19	20-39	40-59	60-79	80-99	100 a.m.	Total
Number families	13	36	21	14	9	2	7	102
% .....	12,7	35,3	20,6	13,7	8,8	2,0	6,9	100,0
Average consumption = 32,3 grs. per man value per day.								

Consumption of *fish* averaged 285 grs. per man value per day. This is the highest value ever found by any dietary investigation in Norway. It is even higher than that found by *Evang*, *Galtung Hansen* and *Lid* in their investigations among Lødingen fisherfolk in 1936. Consumption varied greatly, however, in the different families (table 8), the lowest consumption being 73 grs. and the highest 700 grs. The average consumption of *herring* was 62 grs. per day.

Table 8: *Consumption of fish and fishproducts in the various families.*

Grams per M V per day	< 100	100-199	200-299	300-399	400-499	500 a.m.	Total
Number families	3	21	34	29	10	5	102
% .....	2,9	20,6	33,3	28,4	9,9	4,9	100,0
Average consumption = 284,5 grs. per man value per day.							

*Whole milk* consumption was 256 grs. per man value per day. This is a very low value; it is the lowest on record with the exception of that found by the investigations made in 1912-13 by the Central Bureau of Statistics. It must, however, be remembered that our material comprised relatively few children, and in such material, even in normal times, one would find a low consumption of whole milk, though not so low as in this investigation. Of the 102 families examined, 28 (or 27,5 %) consumed no whole milk during the period of investigation (table 9). The highest consumption was 964 grs. per day; by a woman who, because she was dyspeptic, had an extra ration of milk.

Table 9: *Consumption of whole milk in the various families.*

Grams per M V per day	<100	100- 199	200- 299	300- 399	400- 499	500- 599	600- 699	700- 1000	Total
Number families	28 <sup>1</sup>	13	25	23	2	4	1	6	102
% .....	27,5	12,8	24,5	22,5	2,0	3,9	1,0	5,8	100,0
Average consumption = 255,7 cc per man value per day.									

<sup>1</sup> Includes 11 who had 0 consumption.

The mean consumption of *skimmed milk* was 130 grs. per man value per day. As already mentioned, this represents an increase over the pre-war consumption. As for Oslo, it is necessary to go back to the First World War and rationing to find such a high consumption of skimmed milk. In the individual families consumption ranged from 0 to 384 grs. (table 10).

Table 10: *Consumption of skimmed milk in the various families.*

Grams per M V per day	<100	100-199	200-299	300-399	Total
Number families	45 <sup>1</sup>	32	21	4	102
% .....	44,1	31,3	20,7	3,9	100,0
Average consumption = 130,3 grs. per man value per day.					

<sup>1</sup> Includes 6 who had 0 consumption.

Consumption of *milk of all sorts* averaged 404 grs. per man value per day. This is the lowest value ever found by any previous investigation; even the families on relief who were examined by *Evang* and *Galtung Hansen* in 1933, had a higher consumption. Table 11 shows how consumption varied in the different families.

Table 11: *Consumption of total milk in the various families.*

Grams per M V per day	<100	100- 199	200- 299	300- 399	400- 499	500- 599	600- 699	700 a. m.	Total
Number families	2	8	16	30	24	11	4	7	102
% .....	2,0	7,8	15,7	29,4	23,5	10,8	3,9	6,9	100,0
Average consumption = 403,8 grs. per man value per day.									

Consumption of *butter, margarine* and other fat combined averaged 42 grs. per man value per day. Also this represents

Table 12: *Consumption of butter, margarine and other fat in the various families.*

Grams per M V per day	0-19	20-39	40-59*	60-79	80 a.m.	Total
Number families	5	34	51	9	3	102
% .....	4,9	33,3	50,0	8,8	2,9	100,0
Average consumption = 41,7 grs. per man value per day.						

the lowest value any investigation has ever found. But consumption in the various families ranged all the way from 12,7 to 99 grs. (table 12). The latter, very high value was that of a family who, after having had no butter or margarine for a protracted period, bought a quantity after Norways' liberation. In their joy over their regained freedom and the butter, they indulged in the latter for several days. The variation in also other foodstuffs is to a great part due to the fact that their distribution was uneven. For a long time one might be without them and then suddenly procure rations for several weeks at one time, which generally led to increased consumption for the first few days.

There was a very low consumption of *eggs* and *cheese*. About half of the families examined consumed none during the period of examination (tables 13 and 14).

Table 13: *Consumption of cheese in the various families.*

Grams per M V per day	0	1-9	10-19	20-29	30-39	40-49	50 a.m.	Total
Number families	47	15	17	15	4	1	3	102
% .....	46,1	14,7	16,7	14,7	3,9	1,0	2,9	100,0
Average consumption = 10,0 grs. per man value per day.								

Table 14: *Consumption of eggs in the various families.*

Grams per M V per day	0	1-4	5-9	10-14	15-19	20 a.m.	Total
Number families	67	14	11	5	2	3	102
% .....	65,7	13,7	10,8	4,9	2,0	2,9	100,0
Average consumption = 3,0 grs. per man value per day.							

The mean consumption of *flour*, *bread* and *pastry*, calculated as flour, was 354 grs. per man value per day. For Oslo this

Grams per MV per day	<50	50-99	100-149	150-199	200-249	250-299	300-399	400-499	500+	Total
Number families	22	13	13	11	12	11	6	10	4	102
% .....	21,6	12,8	12,8	10,8	11,8	10,8	5,9	9,8	3,9	100

Average consumption = 190,7 grs. per man value per day.

Consumption of *fresh vegetables* was on an average 191 grs., which represents a great increase over findings of earlier investigations. Consumption varied greatly for the different families (table 17).

Of *fruit, berries, jam and fruitjuice*, the consumption averaged 70,9 grs. While this is not in all respects comparable with figures from previous investigations, it is quite a high value. As in the case of vegetables, the results from the various families differed widely (table 18).

Table 18: *Consumption of fruit, berries, jam and juice in the various families.*

Grams per MV per day	0	1-19	20-39	40-59	60-79	80-99	100- 199	200- 299	300 a. m.	Total
Number families ..	9	25	18	15	8	5	13	6	3	102
% .....	8,8	24,5	17,6	14,7	7,8	4,9	12,8	5,9	2,9	100,0
Average consumption = 70,9 grs. per man value per day.										

The mean *sugar* consumption was 34 grs. per day. This figure includes use of syrup, honey and «Snohetta», a spread containing 80 % sugar. Compared with that of prewar years, the sugar consumption is very low; it is practically the same as that found in the typical «Valle diet» described by *Hoye*. Table 19 shows how consumption varied in the different families.

Table 19: *Consumption of sugar and like things in the various families.*

Grams per M V per day	0-9	10-19	20-29	30-39	40-49	50-59	60 a.m.	Total
Number families	4	9	25	29	26	5	4	102
% .....	3,9	8,8	24,5	28,4	25,5	4,9	3,9	100,0
Average consumption = 34,2 grs. per man value per day.								

In table 20 is noted the consumption of the chief foodstuffs in families with and without children under 15 yrs. of age. As will be observed, the consumption of meat, fish and sugar was virtually the same in both groups. Consumption of milk, cereals and potatoes was greatest in families with children

while that of butter, margarine and other fat, fresh vegetables, fruit and berries was highest in childless families.

Table 20: Consumption of foodstuffs in families with and without children under 15 yrs.

	Consumption in 54 families With children under 15 yrs.	Consumption in 47 families Without children under 15 yrs.
Meat, meatproducts .....	32,9	31,9
Fish .....	283	278
Total milk .....	438	357
Butter, margarine a. o. fat .....	41,7	46,1
Bread, flour + meal, as flour computed.	369	331
Potatoes .....	610	582
Fresh vegetables .....	161	224
Fruit, berries, jam and juice .....	52,9	90,0
Sugar .....	34,8	33,4

The diet of the two orphan homes was not the same as that of families. A comparison of the diet of the orphan homes and that of the Arendal-Ilisøy families (table 4) showed that consumption of meat, fish, skimmed milk, condensed milk, eggs and dried vegetables was lower, in some cases much lower, in the orphan homes than in the families.

*Conclusion:* The diet of wartime was characterized by a radical decrease in consumption of butcher's meat, whole milk, cream, cheese, eggs, margarine, berries, fruit, sugar, and coffee. The consumption of skimmed milk and cereals increased, and that of potatoes, fresh vegetables and fish increased considerably.

### The Caloric Value of the Diet.

The net caloric value of the diet is shown in table 21. The results for each separate family have been noted, and afterward the average for each series given. The average for all series has been calculated, though there is some doubt as to this being justifiable in view of the fact that the different series were carried out at different times and under unlike conditions.

In the first investigations made in January 1943 at the Electric Bureau, the caloric intake ranged from 2586 to 4730 calories,

Table 21: *Net calories per man value per day in families investigated.*

Investigation series	Families:																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
E.B. I	4730 <sup>1</sup>	3150	3386	2768	2819	3340	2586	3095	2881	3487	3155	2628	2912	3283			3159 (3046) <sup>2</sup>
- II	3301	3759	3468	2741	3019	3458	3035		3099	2853	3382						3206
- III		3230	2458	2768	2633		2865			3596	2783						2905
- IV			2487	2671	1893		2440		3076	2962	2426						2565
- V		3336	2951	2605	3374	3036	3066		4134	2322	2470			2145	2124	3053	2900
F. I	2532	2678	3027	2821	2762	2764	1935 <sup>3</sup>	1879 <sup>4</sup>	2392	2525	3245						2596 (2750) <sup>5</sup>
- II	3016			3050	2755	2153	2532		2374		2797	2693	2940	3014	2783	2383	2708
- III	2874				2969	2538	2394		2261		2734	2521		2530			2603
A	2435	2065	2603	2388	3248	3228	2796	3663	2861	3530	3228						2913
H	2586	2057	2808	2997	3745	2662	2548	2597	2375								2708
Total 2849 (2849)																	

<sup>1</sup> Wife 6 mos. pregnant. <sup>2</sup> With family no. 1 not included. <sup>3</sup> Shiftwork. <sup>4</sup> Dyspepsia, ate little. <sup>5</sup> With families no. 7 and 8 not included.

Orphan home I, Arendal: 3024 calories per man value per day.

—»— II, Hisøy: 2984

—»—

with an average of 3159 calories. The highest value was found in a family consisting of a man and his six-months pregnant wife. If this family is excluded, the mean for the series is 3046 calories.

The second series was carried out in June 1943. The values for the individual families fluctuated between 2741 and 3759 calories, with an average of 3206 calories.

The third series was undertaken in May 1944. The values for the various families varied between 2458 and 3596 calories, with a mean value of 2905 calories.

The fourth series, which was made in November 1944, ranged from 1893 to 3076 calories and averaged 2565 calories.

The fifth series was carried out in May 1945. In this series also there were great fluctuations, from 2124 to 4134 calories. The average was 2900 calories. In this series, it must be observed, there was a great difference between the families examined before and those after liberation. From table 22 it will be seen that the 4 families investigated before liberation had an average intake of 2312 calories as against 3167 calories of the families whose investigation began after liberation. One also sees that the intake of the greater number of essential foodstuffs was appreciably higher in the latter group than in the former. This is not due to our having accidentally begun the investigations in some families who generally had a lower intake than others. In the previous investigations, these families had not a lower average consumption than the others, hence there must have been something special about the fifth investigation series.

Table 22: *Calorie consumption and average consumption of most important foodstuffs for investigation E. B. V.*

Survey began	Number families	Meat	Fish	Milk	Average consumption per man value per day.					Calo- ries
					Butter and marga- rine	Pota- toes	Vege- tables	Fruit, Berries	Sugar	
Before liberation	4	19,9	204	341	27,2	381	89	31,5	34,3	2312
After liberation	9	84,7	215	322	52,7	527	98	17,1	35,8	3167
Total	13	64,8	212	328	45,2	481	96	21,6	35,4	2900

The probable explanation is that just at that time certain food-stuffs, among others butter and margarine, were procurable, and as people did not consider it necessary to hoard the supplies after liberation, they ate larger quantities.

The first investigation series at Freia was carried out in November-December 1942. Individual consumption ranged from 1879 to 3245 calories, and the average was 2596 calories. Two of the families had a particularly low consumption, the one 1879 and the other 1935 calories. On looking into the matter they were found to be 2 women who lived alone. One suffered from dyspepsia and consequently ate little—only now and then taking the lunch served at the factory. The other had shiftwork, and as this made it difficult for her to stand in food queues, she ate little. If these 2 „families,, are not included, intake varies from 2392 to 3245 calories, with a mean of 2750 calories.

The second series was undertaken in October-November 1943. The results ranged from 2153 to 3050 calories and the average was 2708 calories.

The third series took place in May 1944 (simultaneously with the fourth series at the Electric Bureau) and varied from 2261 to 2969 calories, with a mean of 2603 calories. The average values agree very well with the corresponding values for the series carried on at the same time at the Electric Bureau (2565 calories). Both are the lowest values found and seem to indicate that the food situation was worse at this time than at the time of the other investigations.

The investigations at Arendal and Hisøy were undertaken in November 1943. The average for the former was 2913 calories, and for the latter 2708. For the 2 orphan homes the figures were 3024 calories and 2984 calories.

The average for all the investigations was 2849 calories whether or not one included the 3 afore-mentioned families.

How do these results accord with findings of earlier investigations in Norway? Table 23 compares our results with those of other investigators. In order to make the results as nearly as possible comparable, we have re-calculated the findings of the others following the same method used in our investigations. We have, however, allowed for 5 % waste for the other investi-

Table 23. *Number of net calories per man value per day for series of Norwegian diet-investigations.*

Investigator, yr.	Number families	Net calories per man value per day
Hertzberg 1930-31 .....	35	3133
Evang and Galtung Hansen 1933 .....		
Entirely on relief .....	92	2538
Partially on relief .....	129	2717
Self-supporting .....	62	3185
All .....		2775
Evang a. o., Bjarkoy 1935-36 .....	5	3067
Evang a. o., Lodingen 1936-37 .....	22	3262
Evang and Galtung Hansen Oslo 1936-37		
On relief .....	16	2520
Self-supporting .....	14	3379
Hoye, Valle 1937-38 .....	10	3307
Storstein, Skånland 1938 .....	9	3658
Own investigations		
E. B. I .....	13	3064
- II .....	10	3206
- III .....	7	2905
- IV .....	7	2565
- V .....	13	2900
- VI .....	9	2750
F. I .....	12	2708
- II .....	8	2603
- III .....	11	2913
Arendal .....	9	2708
Hisoy .....		

gations as against 2 % for ours inasmuch as the waste was undoubtedly greater before the war than during its progress. It is evident from the table that previous to the war self-supporting families consumed, on an average, from 3100 to 3600 calories daily. Those of very limited means consumed less. The lowest values were found by *Evang and Galtung Hansen* in 1933 among families on relief (2282 calories).

On comparing these values with those found by us we see that, excepting the first 2 series at the Electric Bureau, our values are lower—in some cases considerably lower—than the values self-supporting families had before the war. Thus the calorie intake noted in May 1944 (Electric Bureau IV and Freia III) was about 2500-2600 calories, i. e. approximately

that which *Evang* and *Galtung Hansen* found among those partially on relief in 1933, and for those entirely on relief in Oslo 1936-37.

A comparison with international standards gives the same result. In table 24 is shown the number of calories that our families should have had according to two of the best known standards: that of the Health Committee of the League of Nations and that of the Food and Nutrition Board, National Research Council, Washington 1945. The table also shows how large the intake should have been according to the two diets proposed by the Oslo Committee of 1936\* and the State Food Council of 1939.

According to all these proposals the requirements of the families should have been about 3000-3500 calories per day,

Table 24. *Calorie consumption in our investigations compared with consumption calculated on basis of N. F.'s standard, American standard and two Norwegian dietary plans.*

Net calorie consumption per man value per day.					
Investi- gations	N. F.s standard <sup>1</sup> 1936	American standard <sup>2</sup> 1945	Oslo Com- mittee's plan <sup>3</sup> 1936	State Food Council <sup>4</sup> 1939	Own investigations
E. B. I	3097	3061	3055	3162	3046
- II	3198	3139	3131	3244	3206
- III	3170	3150	3148	3240	2905
- IV	3277	3186	3246	3377	2565
- V	3219	3203	3168	3301	2900
F. I	3239	3052	3182	3306	2750
- II	3234	3090	3195	3315	2708
- III	3208	3008	3189	3306	2603
Arendal	3067	3054	3030	3121	2913
Hisøy	3092	3158	3152	3220	2708
	3164	3116	3134	3243	2849

<sup>1</sup> Following supplements for muscular activity: Adults, men 600 calories per day, adults, women 440, boys 11-15 yrs. 400, girls 11-15 yrs. 200 and children 5-11 yrs. 160. <sup>2</sup> Recommended Dietary Allowances. Food and Nutrition Board, National Research Council, Washington 1945. <sup>3</sup> From the gross values recorded a deduction is made: 5% for waste and 3% for loss in absorption, total 8%. Deduction is probably on highest level. <sup>4</sup> From values given in proposed plans 5% is deducted for waste. Loss in absorption is allowed for in the plan.

\*) The Oslo Committee was appointed by the Oslo Council in 1936 to plan a cheap, but adequate diet for poorer families.

nature. It was primarily rationing which limited the diet and that was advantageous to families with children rather than to those having none. It was thus not to be expected in our investigations that there should be such a great difference between families with children and those without as there had been in previous investigations. Table 25 show that in all investigation series in Oslo, families with children under 15 years had a somewhat higher calorie intake than childless families. The fifth investigation series at E. B. has not been included because of the special conditions which prevailed during this investigation. In the Arendal-Hisoy investigations, the families with children had a lower calorie intake. This is possibly due to the fact that there was a greater number of children in these families than in those living in Oslo, and that lack of money made itself somewhat felt.

Table 26 shows the distribution of the calories on the various food groups. We see that the majority of calories are from the group: Flour, meal, breads and pastry (42,5 %). The second largest quantity came from potatoes (15 %); the fat group supplied 12,2 % and the fish group 8,2 %.

Table 26: *The percentage of protein, fat, carbo-hydrates and calories from the various foodstuffgroups.*

Foodstuffs	Protein	Fat	Carbo-hydrates	Calories
Meat, meatproducts .....	4,68	7,48	0,06	2,49
Fish, fishproducts .....	37,20	13,49	0,35	8,23
Whole milk .....	7,72	12,04	2,61	6,06
Skimmed milk a. o. milk .	4,85	1,31	1,63	2,01
Butter, margarine a.o. fats including cod-liver-oil ...	0,24	50,63	0,04	12,20
Cheese .....	2,13	2,01	0,55	1,12
Eggs .....	0,34	0,42	0	0,15
Flour, meal and bread....	29,85	10,24	57,84	42,48
Potatoes .....	8,62	0	22,28	15,01
Fresh vegetables .....	2,66	0,54	2,88	2,29
Dried vegetables .....	0,96	0,28	0,62	0,59
Fruit, berries etc. ....	0,45	0,75	3,25	2,25
Sugar and similar things ..	0,05	0	7,37	4,57
Sundry .....	0,25	0,81	0,52	0,55
	100,00	100,00	100,00	100,00

*Conclusion:* With the exception of the first two investigation series at E. B., the calorie content of food was clearly lower than that of food which self-supporting families had before the war, and lower than international standards.

### Protein, Fat and Carbohydrates.

In table 27 is recorded the average net consumption of animal and vegetable protein, of total protein and of fat and carbohydrates. The net consumption has been computed by deducting from the gross values first 2 % for waste and thereafter for loss by absorption. *Atwater* places the loss by absorption at 3 % for animal protein, 15 % for vegetable protein, 5 % for fat and 2 % for carbohydrates. The total deduction made is thus: 5 %, 17 %, 7 % and 4 % respectively.

Table 27: *Net consumption of protein, fat and carbo-hydrates.*

Investigations	Animal	Protein Veget.	Total	Fat	Carbo- hydrates
E. B. I . . . . .	61,31	42,69	104,00	77,30	482,12
- II . . . . .	70,19	38,50	108,69	86,92	469,76
- III . . . . .	67,71	35,27	102,98	73,05	433,42
- IV . . . . .	47,53	35,40	82,93	63,09	396,41
- V . . . . .	48,38	37,28	85,66	85,21	423,43
F. I . . . . .	52,35	33,66	86,01	67,98	386,63
- II . . . . .	49,40	34,41	83,81	66,83	418,61
- III . . . . .	70,51	30,90	101,41	69,03	370,63
Arendal . . . . .	50,60	37,25	87,85	63,15	473,07
Hisoy . . . . .	46,59	35,68	82,27	61,11	433,49
Average . . . . .	56,45	36,10	92,55	71,37	428,76
Orphan home I	29,23	44,84	74,07	70,83	560,99
—»— II	35,63	48,53	84,16	79,36	519,94

Table 28: *The proportion (in percentage) of net calories in protein, fat and carbo-hydrates.*

		Electric Bureau					Freia					Total
		I	II	III	IV	V	I	II	III	A	H	
Percentage of net calories from	P	14,3	14,7	15,4	14,0	12,8	14,4	13,4	16,8	13,1	13,2	14,2
	F	23,1	25,5	23,7	23,1	27,6	24,7	23,3	25,0	20,4	21,3	23,8
	CH	62,6	59,8	61,0	62,9	59,6	60,9	63,3	58,2	66,5	65,5	62,0

Table 28 shows what percent of the net calories is derived from protein, fat and carbo-hydrates. In working out this table it has been assumed that 1 gram of *absorbed* protein gives 4,35 calories, 1 gram of fat 9,45 calories and 1 gram of carbo-hydrates 4,10 calories.

### *Protein.*

It will be seen from table 27 that the net consumption of protein per man value per day ranged from 82,27 grams to 108,69 grams with a mean intake of 92,55 grams.

These values are satisfactory. Although the protein requirement is not definitely known, the majority consider that in these latitudes it should be somewhere between 70 and 100 grams per man value per day, corresponding to about 10 or 13 % of the calorie requirement. As vegetable protein generally has a lower biological value than animal, it is assumed that one third to one half of the protein should be of animal origin. It will be seen that these demands are entirely satisfied in our investigations. As the total calorie intake is comparatively low, a relatively large proportion of the calories come from protein. In the individual investigation series, the percentage varied between 12,8 and 16,8 % and the mean was 14,2 % (see table 28).

Table 26 shows that it was first of all fish and cereals which provided protein, with milk and potatoes ranking second.

### *Fat.*

As is apparent from table 27, the net consumption of fat in our investigations varied from 61,11 grams to 86,92 grams, with an average of 71,37 grams per man value per day. 23,8 % of the calories proceeded from the fat.

These values are low. The data at present available do not suffice to permit a precise statement of the quantity required. But in all the diets which have previously been investigated in Norway and which have been characterized as satisfactory, fat consumption has been considerably higher. The same has also been true of the different diets proposed.

In table 29 is shown the net consumption of protein, fat and carbo-hydrates found in some investigations in Norway. It will

be seen that the fat consumption of the self-supporting families was on an average, about 80 to 100 grams per day. Our figures are lower and are only slightly higher than the figures for the families entirely on relief (1933).

The table also shows the fat content in some dietary plans. Of these have been chosen *Hazel Stiebling's* 4 dietary plans for families of modest incomes, converted by *Evang* and *Galtung Hansen* to Cathcart's scale, and plans by the British Medical Ass., «The Oslo Committee» and the «State Food Council». It is evident from this table that all these proposals have a greater fat content than that found in our investigations.

From table 26 we see that approximately half the fat in the food originated in the group: butter, margarine (and other fats) + liver oil, the second most important source of fat was fish, thereafter whole milk and the flour-bread group.

#### *Carbo-hydrates.*

The net consumption of carbo-hydrates in our investigations was, as shown in table 29, between 371 and 482 grams per man value per day, and averaged 429 grams, corresponding to 62 % of the calorie intake.

There is nothing remarkable about the figures in themselves. Table 29 shows that previous investigations of diet have found higher as well as lower carbo-hydrate intake. As, however, our investigations found a comparatively low calorie intake, the carbohydrate consumption was relatively high. As will be remarked from the table, it was only in a comparatively few of the earlier investigations that carbo-hydrates provided as much as 62 % of the calories. It is especially noteworthy that the greater number of proposed dietaries give carbo-hydrates a more modest place.

As was to be expected, the flour-bread group, potatoes and, to a lesser extent, sugar supplied the greater part of the carbo-hydrates (table 26).

*Conclusion:* The diet was relatively deficient in fats. The intake of protein and carbo-hydrates was, on the whole, adequate. It was chiefly deficient fat intake which caused the number of calories in the diet to be low.

Table 29: *Consumption of protein, fat and carbo-hydrates in various dietary investigations and proposed diets.*

Investigator and year	Grams per man value per day (net values)			Percent of net calories from:		
	P	F	CH	P	F	CH
Statistic Central Bureau 1927-28				12,0	36,7	51,3
Hertzberg 1931 .....	98,7	109,5	408,1	13,7	33,0	53,3
Evang and Galtung Hansen 1933						
Entirely on relief .....	55,0	71,2	354,4	10,1	28,4	61,4
Partially on relief .....	66,6	77,5	414,7	10,6	26,9	62,5
Self-supporting .....	82,2	95,9	470,1	11,2	28,4	60,4
Høye 1937-38 .....	119,3	86,9	481,4	15,7	24,8	59,5
Storstein 1938 .....	130,0	93,3	541,7	15,4	24,1	60,6
Strom 1942-45 .....	92,6	71,4	428,8	14,2	23,8	62,0
Stiebling's proposed dietary I	66,9	84,0	385	10,4	29,7	59,9
—»— II	85,9	116,8	383	11,7	36,1	52,2
—»— III	82,0	127,5	362	11,2	39,4	49,4
—»— IV	86,9	143,5	307	12,1	45,2	42,7
British medical						
Assoc.'s proposal .....	81,5	87,0	450	11,1	27,1	61,7
Oslo Committee's proposal ...	101	111	406	14,0	33,3	52,7
State Food Council's proposal .	108	132	375	14,4	38,3	47,3

## Minerals.

While the protein, fat and carbo-hydrate content of a diet can be calculated with reasonable accuracy, great difficulties are encountered in computing the amount of minerals and vitamins. Concerning the amount of these stuffs to be found in food we have only a limited knowledge, especially with respect to the great variations which exist. Nor do we know enough about loss through waste and imperfect absorption to calculate the net intake. In addition we lack the required knowledge of the requirements of the different age-groups to prepare correct man value scales.

The scales which we employ for the calories are not rational when minerals and vitamins are in question inasmuch as the relation between the requirements in the various age-classes is different for minerals and vitamins from what it is for calories. But lacking more suitable scales, those for calories have been used. For comparative investigations they can be employed

with certain reservations. But in addition one frequently computes the intake per individual per day, which method is, in many cases, as satisfactory as the former.

In our investigations, the mineral and vitamine content of the diet has been computed by both methods. The figures adduced in the following are the gross mineral and vitamine content of the diet.

### *Calcium.*

The average calcium content of the diet in the various investigation series will be seen in table 30. Calculated per man value the daily amount varied from 1,12 to 1,53 grams, with an average of 1,32 grams for the total series. Computed per individual, the amount varied from 0,96 grams to 1,28 grams and had a mean of 1,11 grams per day.

Table 30: *Average consumption of calcium, phosphorus and iron.*

Investigations	Per man value per day			Per person per day		
	Ca gram	P gram	Fe mg	Ca gram	P gram	Fe mg
E. B. I <sup>1</sup> . . . . .	1,53	2,22	15,58	1,28	1,86	13,08
- II . . . . .	1,40	2,18	16,58	1,21	1,89	14,33
- III . . . . .	1,30	2,15	14,67	1,14	1,89	12,94
- IV . . . . .	1,17	1,82	13,27	1,02	1,59	11,60
- V . . . . .	1,30	1,89	13,57	1,14	1,65	11,86
F. I . . . . .	1,33	1,74	13,21	1,13	1,47	11,18
- II . . . . .	1,26	1,81	12,90	1,05	1,51	10,79
- III . . . . .	1,12	1,84	13,51	0,96	1,57	11,55
Arendal . . . . .	1,38	1,97	16,28	1,12	1,60	13,23
Hisoy . . . . .	1,29	1,88	14,52	1,02	1,49	11,51
Total . . . . .	1,32	1,95	14,46	1,11	1,65	12,20
Orphan home I	1,75	2,10	17,20	1,38	1,59	13,61
- II	1,45	2,19	18,04	1,10	1,66	13,64

<sup>1</sup> Excluding family I, the figures are: 1,46 2,15 15,20 and 1,22 1,80 12,69.

These values may be regarded as very good. Table 31 compares our values with the results of other diet investigations in Norway. It appears from the table that the calcium consumption in our investigations is about the same as the consumption of self-supporting families in the investigations made by *Evang* and *Gallung Hansen* (1933) and considerably better than that

of families on relief. *Storstein's* figures are also lower than ours. *Høye's* figures are exceptional, due to the very great consumption of skimmed milk in the Valle dietary.

Table 31: *Content of minerals in the diet in some Norwegian dietary investigations.*

Investigators	Per man value per day		
	Gram Ca	Gram P	Mg Fe
Evang and Galtung Hansen 1933			
Entirely on relief .....	0,85	1,22	5,91
Partly on relief .....	1,14	1,43	7,00
Self-supporting .....	1,42	1,71	8,26
All .....	1,11	1,43	6,93
Høye 1937-38 .....	2,58	3,14	62,00
Storstein 1938 .....	1,21	1,73	21,60
Strom 1942-45 .....	1,32	1,95	14,46

Also compared with the current standards our values are gratifying. For comparison we have chosen the standards of the Food and Nutrition Board and those of *Leitch*.

*Leitch* sets the calcium requirement for children under 9 years at 0,9 grams per day; it increases thereafter to circa

Table 32: *Calcium and iron content of food compared with content computed on basis of different standards.*

Investi- gations	Grams calcium per person per day			Mg. iron per person per day		
	Require- ment acc. to Leitch	acc. to Leitch with 50% suppl.	American standard	Content of diet	American standard	Content of diet
E. B. I	0,73	1,10	0,92	1,22	11,71	13,08
- II	0,73	1,10	0,96	1,21	11,92	14,33
- III	0,73	1,10	0,94	1,14	12,24	12,94
- IV	0,68	1,02	0,90	1,02	12,13	11,60
- V	0,75	1,13	0,94	1,14	12,22	11,86
F. I	0,63	0,95	0,86	1,13	11,83	11,27
- II	0,60	0,90	0,87	1,05	12,00	10,79
- III	0,61	0,92	0,85	0,96	12,08	11,55
Arendal	0,87	1,31	0,98	1,12	11,72	13,23
Hisøy	0,88	1,32	1,03	1,02	11,96	11,51
Total	0,72	1,08	0,94	1,11	11,95	12,20

[illegible]

*Phosphorus.*

According to table 30, the mean intake of phosphorus, in all the investigation series, was 1,95 grams per man value per day, and varied between 1,74 and 2,22 grams. Calculated per individual, the average was 1,65 grams and ranged from 1,47 to 1,89 grams.

These values are very satisfactory. As shown by table 31, the phosphorus intake found in our investigations was higher than in those previously undertaken in Norway, with the exception of those made by *Hoye*, in which as before stated, special conditions prevailed.

Of the various standards for phosphorus intake, the best known is *Sherman's*. He sets the requirement for an adult at .88 grams per day and reckons that the intake should be 50 % higher, i. e. 1,32 grams per day. Growing children presumably need at least as much phosphorus as adults. The Food and Nutrition Board indicates that for children, pregnant and nursing women the phosphorus intake should be as great as that of calcium. For other adults it should be  $1\frac{1}{2}$  times as great. Table 30 shows that these requirements were met in our investigations.

*Iron.*

The iron intake averaged 14,46 mg per man value per day, and ranged from 12,90 to 16,28 mg. Computed per individual there was a mean of 12,20 mg and variations from 10,79 mg to 14,33 mg.

These values are not particularly high. Table 31 shows that the average for our investigations is higher than the figures for the investigations by *Evang* and *Galtung Hansen* in 1933 (also the self-supporting), but considerably lower than the results of *Storstein* and *Hoye*.

A comparison with the American standards shows that for the combined series, the iron intake was gratifying in our investigations (table 32). But it is apparent from the table that in 6 of the series, the iron content of food was below the standards.

Due to the great uncertainty which prevails regarding the calculation of the mineral content of food, and want of knowledge as to the requirement, sweeping conclusions should not

be drawn from such a result as this. But it should be stated in this connection that mild cases of anemia were frequent in Oslo during the war.

The intake was found to be more satisfactory for the orphan homes than for the families.

According to table 33, flour and pastry supplied the most iron, while potatoes and fish ranked second.

*Conclusion:* The average calcium and phosphorus content of the diet was satisfactory while the iron content appeared to be low.

### Vitamines.

As stated in the section on minerals the vitamine content of food is computed both per man value and per individual. The figures given are gross values.

#### *Vitamine A.*

The vitamine A content of the diet will be seen from table 34. The average content per man value was 4911 I. U. and varied

Table 34: *Vitamine content of diet.*

Investi- gation series	Per man value per day				Per person per day				Animal vit. A in pct. of total vit. A
	A I. U.	B <sub>1</sub> I. U.	C mg.	D I. U.	A I. U.	B <sub>1</sub> I. U.	C mg.	D I. U.	
E. B. I	10029	848	103	1879	8424	712	87	1578	90,1
- II	3170	789	40	1298	2742	682	34	1122	79,7
- III	3565	723	44	1635	3155	624	38	1441	91,0
- IV	5223	734	94	849	4582	645	82	743	55,4
- V	2011	722	49	942	1764	640	43	823	55,6
F. I	6850	616	134	1170	5805	521	113	991	80,3
- II	2957	660	193	715	2464	562	162	598	54,1
- III	3235	621	60	1192	2765	531	51	1019	80,7
Arendal	4239	761	121	525	3446	627	98	427	47,8
Hisoy	6568	705	109	802	5213	577	86	636	71,8
	4911	720	98	1107	4162	612	83	935	72,9
Orphan- home I	15784	881	241	1554	12524	697	191	1230	88,5
Orphan- home II	6745	889	176	511	5110	672	133	386	40,7

from 2011 I. U. to 10029 I. U. Computed per individual the mean was 4162 I. U. with variations from 1764 to 8424 I. U. For computing these figures it was estimated that carotene had half the value of vitamine A.

As average values these must be regarded as good, even though they do not satisfy the highest standards given. One generally reckons 1000 to 1500 I. U. as the minimum vitamine A requirement, the optimum requirement varies from 2000 to 8000 I. U., or even higher. The American standards thus put the requirement at 5000 I. U. for adults (males or females), and 1500 to 6000 I. U. for children; for pregnant and nursing women 6000 and 8000 I. U. respectively are needed. These standards are based on the assumption that  $\frac{2}{3}$  of the units come from carotene and  $\frac{1}{3}$  from vitamine A, and further that carotene has a value equivalent to half, or less, the value of vitamine A.

Table 35 shows how much vitamine A the families in our investigations should have had according to the American standards, and compares that with the amount the food actually contained. As the diet in our investigations was relatively richer in vitamine A and poorer in carotene than presupposed by the standards a recalculation of the standards was done.

Table 35: *Vitamine intake for our investigations compared with intake computed on basis of American standards.*

Investigation series	Vitamine A		Vitamine B <sub>1</sub>		Vitamine D	
	American standards	Content of diet	American standards <sup>1</sup>	Content of diet	American standards	Content of diet
E. B. I	3320	8424	381	712	71	87
- II	3672	2742	393	682	74	34
- III	3459	3155	396	624	74	38
- IV	4303	4582	390	645	73	82
- V	4309	1764	399	640	74	43
F. I	3666	5805	378	521	70	113
- II	4331	2464	378	562	71	162
- III	3745	2765	378	531	71	51
Arendal	4143	3446	372	627	71	98
Hisoy	3629	5213	366	577	71	86
	3839	4162	384	612	72	83

<sup>1</sup> On converting mg. to I. U., 300 I. U. has been allowed for 1 mg.

The table shows that in 4 of the 10 series, the vitamine A content was higher than that required by the standards, and in 6 it was lower. The average for the combined investigations was slightly above the standards.

As the American standards must be regarded as relatively high, these results are quite satisfactory. In some of the series, however, the intake was low. This is particularly true of investigation V at the Electric Bureau, in which the intake was 1764 I. U. per person per day, and of the investigation II at Freia, in which it was 2464 I. U. per person per day.

An investigation of the consumption in the different families showed great variations also in the same investigation series. Cod-liver-oil consumption was chiefly responsible for these differences. In table 36 the families are grouped according to their vitamine A intake. We see that during the period of investigation 19 families (or 18,6 %) had an intake of less than 1000 I. U. per person per day and 29 families (28,4 %) an intake of 1000 to 2000 I. U. per person per day. Although great uncertainty is naturally associated with the computation of the vitamine A intake, and although the requirement for individuals indubitably varies greatly, these results nevertheless indicate that the intake for some families was very low. This agrees with *Hovind's* findings. He examined the employees of the Electric Bureau and Freia during the autumn of 1943 and spring of 1944 and found a high incidence of nightblindness, though it was fairly mild. On the other hand, there is no doubt that a large proportion of the families had a very generous intake of vitamine A.

Table 36: *Consumption of vitamine A in the various families.*

I. U. vit. A per person per day	No. families	%
Under 1000	19	18,6
1000-1999	29	28,4
2000-2999	13	12,7
3000-3999	6	5,9
4000-4999	7	6,9
5000 or more	28	27,5
	. 102	100,0

*Vitamine B<sub>1</sub> (aneurin).*

Table 34 shows that the average aneurin content of the diet was 720 I. U. per man value per day, and ranged from 616 to 848 I. U. Calculated per person, the average was 612 I. U.; the lowest value was 521 I. U. and the highest 712 I. U.

These values are very high and exceed even those of the American standards (table 35). It is apparent from table 37 that only 5 families, or 4,9 %, had an intake below 400 I. U. per person per day, and that about  $\frac{2}{3}$  had from 500 to 700 I. U.

Table 37: Consumption of aneurin in the various families.

I. U. aneurin per person per day	No. families	%
Under 400	5	4,9
400-499	12	11,8
500-599	34	33,3
600-699	31	30,4
700-799	12	11,8
800 or more	8	7,8
	102	100,0

These results are interesting. During the war there was much talk to the effect that the diet contained too little aneurin, and it was thought that this was one of the causal factors in a succession of obscure clinical pictures in which there was a tendency toward oedema, frequent nismus etc.

Our findings do not support this view and while one should be cautious about generalizing on the basis of our few investigations, there are no food investigations that show the war-time food to have been deficient in aneurin. Galtung Hansen has informed us verbally that also his investigations found a high aneurin content in the food.

*Vitamine C.*

The average vitamine C content was 98 mg ascorbic acid per man value per day and it ranged from 40 to 193 mg. Calculated per person per day, the mean was 83 mg and varied from 34 to 162 mg.

Table 38: *Consumption of Vitamine C in the various families.*

Mg. vit. C per person per day	No. families	%
Under 30	7	6,8
30-59	37	36,3
60-89	21	20,6
90-119	15	14,7
120-149	10	9,8
150 or more	12	11,8
	102	100,0

If, as is generally done in this country, the optimum ascorbic acid requirement per day is set at 30-50 mg, our findings must be considered satisfactory. The mean is far in excess of the optimum requirement and, as will be seen from table 38, there were only a few families whose intake was less than 30 mg per person per day.

If, however, we accept the American standards the case is altered, inasmuch as several of our investigations showed that the ascorbic-acid content fell short of the standards (table 35). But the American standards are exceptionally high, and it is probable that one can manage quite well with considerably less.

Table 33 shows that it was potatoes and fresh vegetables which supplied the greater part of the ascorbic acid.

#### *Vitamine D.*

The mean vitamine D content was 1107 I. U. per man value per day, and it varied from 525 to 1879 I. U. Computed per person per day, the content varied from 427 to 1578 I. U. and averaged 935 I. U.

Also these values must be regarded as satisfactory. According to the American standards the requirement for children over 1 year is 400 I. U., for pregnant and nursing women as well as infants 400-800 I. U., and for other adults it is «small quantities for those not exposed to the sun».

These requirements should, on the whole, be well fulfilled in the dietary of our families, especially when one takes into consideration that these families consisted mainly of adults.

Table 39: *Consumption of vitamine D in the various families.*

I. U. vit. D per person per day	No. families	%
Under 200	9	8,8
200-399	11	10,8
400-599	15	14,7
600-799	22	21,6
800 or more	45	44,1
	102	100,0

As shown in table 39, the majority of our families had an intake above 400 I. U.; and 44 % had an average intake of more than 800 I. U.

Table 33 shows that a good  $\frac{2}{3}$  of the vitamine D was supplied by fish—first and foremost herring— and about 30 % by cod-liver-oil. The amount of D vitamine furnished by other food-stuffs was insignificant.

*Conclusion:* The average vitamine consumption must be regarded as satisfactory. The vitamine intake in the various families differed widely, however, and it is probable that some families may have had less than the amount requisite. This applies particularly to vitamine A.

## General Discussion.

The number of families in our investigations is small and the group is not, strictly speaking, representative of anything other than itself. There is, however, much that warrants the drawing of somewhat more extreme conclusions from the investigations than the number of families would seem to justify.

Firstly, there can be not doubt that as regards consumption of individual foodstuffs, the results agree well with the diet on which the Oslo people lived during the war, and with that which rationing allowed. Secondly, the findings are supported by clinical experiences.

As has been mentioned, a loss of weight was very common

in Oslo during the years in which the investigations were undertaken; the majority of people lost several kilos in weight. As an example may be adduced the average weight of the employ-ées at Freia chocolate factory:

	1940	1941	1942	1943	1944	1945
Men	71,6	71,0	69,4	68,9	69,8	70,1
Women	61,7	61,5	60,7	60,7	60,8	61,7

At other concerns the loss of weight was greater, but nowhere was there any question of famine. This accords well with the fact that our investigations found the calorie intake to be lower than it had been for self-supporting families prior to the war, but that there were no extremely low values.

While loss of weight was frequent, clearly defined deficiency diseases were rare. There was a certain tendency to anemia, and *Hovind's* investigations showed that a mild degree of night-blindness prevailed. This is in complete accordance with our findings.

We are therefore of the opinion that notwithstanding the small number of families participating in our investigations, they give a quite good idea of the war dietary of the workers in Oslo, i. e. of a large proportion of the population of Oslo.

We must further remember that the difficulties attendant on procuring a fully normal diet during the war, were indubitably greater in Oslo than in other parts of the country. We again experienced, during the war, that it is the cities—and chiefly the larger ones— which suffer most in such times.

When the food conditions in Oslo nevertheless proved to be relatively satisfactory, one should not be unjustified in concluding that, as regards food, Norway got off surprisingly lightly from the war and occupation. This does not preclude the possibility that certain groups may have had a less satisfactory diet; for older people living alone and for families with many half-grown children the situation was without doubt very difficult until 1944, when soup was distributed. But on the whole, conditions were better than might have been expected.

## Summary.

The author has undertaken diet investigations among families at 2 industrial concerns in Oslo (Electric Bureau and Freia) and among some few families in Arendal and Hisøy. At the Electric Bureau, 5 different investigations were carried out from Jan. 1943 to May 1945. At Freia there were 3 investigations from Dec. 1942 to May 1944, and in Arendal and Hisøy 1 investigation series in November and December 1943. The number of families participating in the various investigation series was 14, 10, 7, 7, 13, 11, 12, 8, 11 and 9 respectively, a total of 102. The investigated families, especially in the Oslo material, were for the greater part small and with few children. In Arendal and Hisøy, also 2 orphan homes were examined.

The periods of investigation were of 14 days duration. The families' consumption of food during the period was determined in the following manner: a daily account was kept of the food purchased and received, as well as of the food which was brought out of the house. The food supply was weighed at the beginning and again at the close of the period. In computing, Catchart and Murray's scale was used. 2 % was allowed for waste in housekeeping, excepting for the orphan homes where the waste was fixed at 10 %. In calculating the caloric intake Atwater's figures: 4-9-4 were used.

Compared with pre-war food, the diet of the investigated families was characterized by a great decrease in consumption of meat, whole milk, cream, cheese, eggs, margarine (but not butter), fruit, berries, sugar and coffee. The consumption of skimmed milk increased, though not sufficiently to compensate for the decrease in consumption of whole milk. The consumption of cereals was somewhat greater and that of potatoes, fresh vegetables and fish was much greater.

The mean caloric content of the diet, in the various investigation series, was: 3046, 3206, 2905, 2565, 2900, 2750, 2708, 2603, 2913 and 2708 net calories. The total average was 2849 calories. Excepting the first 2 series, all these figures are lower than those of self-supporting families in this country before the war, and of the families investigated during the latter half of

May 1945. The figures are also lower than the most commonly used international standards.

The protein content of the diet varied between 82 gr. and 109 gr. with a total average of 93 gr. Correspondingly, the fat content varied from 61 to 82 gr., and averaged 71 gr. The extremes of carbo-hydrates were 372 and 482 gr., with a mean of 429 gr. Compared with previously investigated diets in Norway, and with international standards, the intake of protein and carbo-hydrates was satisfactory while that of fats was low. It was primarily deficient fat-intake which caused the calorie intake to be low in the majority of investigation series.

The gross calcium content varied in the different investigation series from 1,12 gr. to 1,53 gr. per man value per day, and the total average was 1,32 gr. Corresponding figures for phosphorus were 1,74 and 2,22 gr., with an average of 1,95 gr. The iron content ranged from 12,90 to 16,28 mg., with a mean of 14,46 mg., Compared with previous investigations and standards, the average calcium and phosphorus content must be considered satisfactory while the intake of iron seemed to be below the requirements.

The gross vitamine intake per man value per day, was;

Vitamine A: average 4911 I. U., lowest series 2011 I. U., highest series 10 029 I. U.

— B<sub>1</sub>: average 720 I. U., lowest series 616 I. U., highest series 848 I. U.

— C: average 98 mg., lowest series 40 mg., highest series 193 mg.

— D: average 1107 I. U., lowest series 525 I. U., highest 1879 I. U.

The average values for the greater number of series must be characterized as satisfactory, in part, very satisfactory. There were, however, great variations in the vitamine intake of the individual families and it is thus probable that some families were below the optimum requirement. This was especially true of vitamine A.

The author is of the opinion that even though the number of families investigated was small, the findings give a quite good idea of the diet of workers and functionaries in Oslo during the war.

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